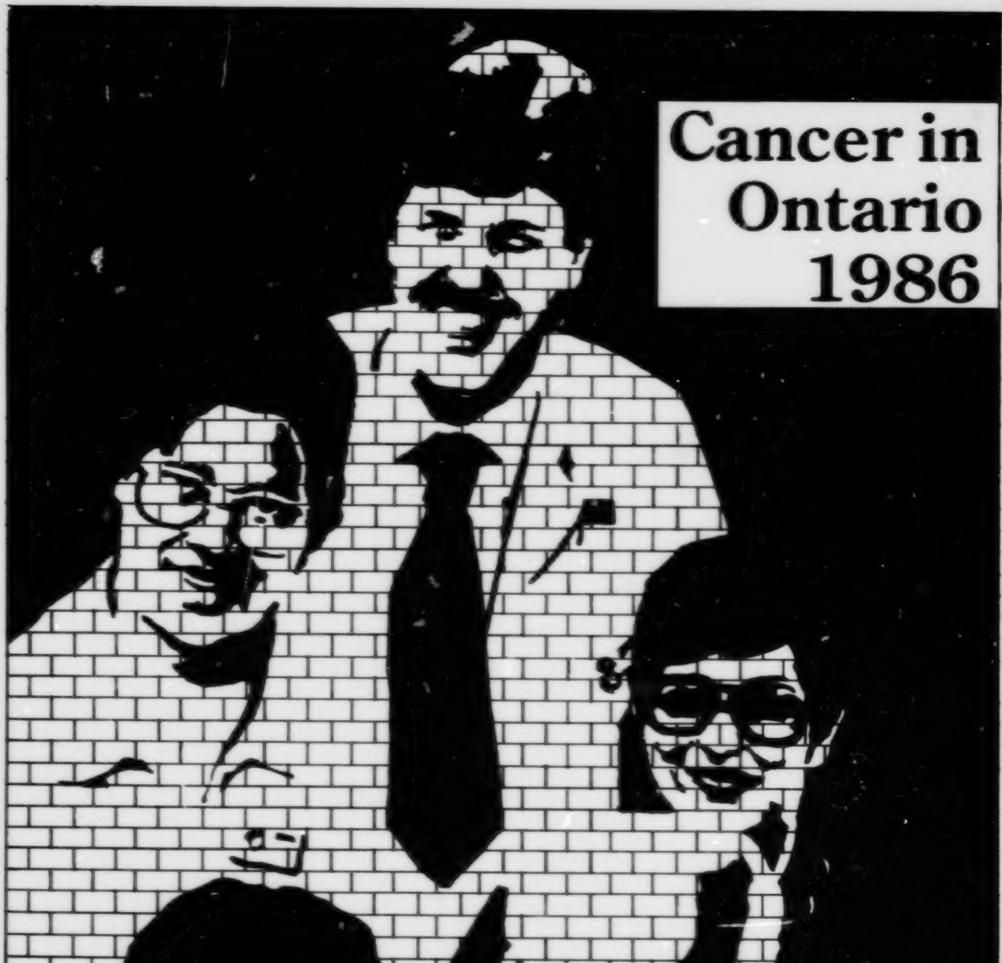
Cancer in Ontario 1986



OCF

The Ontario Cancer Treatment and Research Foundation

87-06036/

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

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CANCER IN ONTARIO

1986

THE COVER

This year the cover seeks to emphasize the primacy of human beings in cancer care. The theme of *Cancer in Ontario* 1986 is "more than bricks and mortar": large sums have been allocated to build new buildings and to purchase new treatment machines but less attention has been directed at the acquisition, training and day-to-day support of the many kinds of health-care professionals who man the complex system, which is modern cancer control. The cover acknowledges the importance of bricks --showing two walls but focusses on a group of people trained for modern cancer care: behind both, but unseen, are the swelling multitudes of those in Ontario who have cancer or in the near future will develop some form of the disease.

The Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard
Toronto, Ontario, Canada
M4H 1A8

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MESSAGE FROM THE CHAIRMAN

Photo: Tony V. Hauser

1986 has been another year of challenge for the Ontario Cancer Treatment and Research Foundation.

The continued increase in the number of cancer patients and our wish to provide them with first-class care has placed severe strains on existing facilities and finances. I am pleased to report that the Government of Ontario recently has provided major funding in both areas which has done much to alleviate our immediate problems.

In turn and in concert with the Ontario Cancer Institute incorporating the Princess Margaret Hospital (OCI/PMH) and the Canadian Cancer Society Ontario Division, we have made an unprecedented commitment to raise $50 million over the next three to five years for capital purposes.

In 1985, the Provincial Role Study of Cancer Services in Ontario recommended a merger of the OCI/PMH and the Foundation into one "Ontario Cancer Agency". Talks now in progress are aimed at achieving this goal.

Governance of the Foundation would not be possible without the dedicated support of its Board Members. I am pleased to report the reappointment during 1986 of Mr. G. Adams, Mr. G.P. Eligh, Dr. G.D. Hurteau, and Dr. G.R. Walker. We welcomed as new Members Mrs. B. Johnston, Dr. N. Pohran, Mrs. I. Rubin, Mr. C. Waxman, and Dr. J.Y.K. Wong. During 1986, Mr. R.W. Stevens and Mr. W.A. Wilkinson retired after making major contributions to the Foundation over many years. To them we are deeply grateful.

In closing I wish to thank: The staff of our eight Centres and Head Office for their dedicated service in spite of many difficulties; the Canadian Cancer Society Ontario Division for their financial and volunteer support, without which we could not offer the level of programs that exist today; and finally the people of Ontario through their Government, without whose continued support we would not exist.

Michael A. Meighen
Chairman

EXECUTIVE DIRECTOR REPORTS

The heart of the Foundation is its people. Without them we could not carry out our programs of prevention, treatment, research and education, which are directed to the best possible care for the cancer patients of Ontario. Our staff now numbers approximately 900 people who are located in nine geographic sites – a diffusion which presents major challenges in co-operative planning and management. I cannot acknowledge everyone but wish to thank all the staff for their support. In particular, I note the appointment in 1986 of Dr. R.E.T. Corringham as the Director of the Northeastern Ontario Oncology Program (soon to become the Northeastern Ontario Cancer Centre) and the appointment of Dr. L. Levin as Director of the London Regional Cancer Centre (effective April 1, 1987). While not effective until 1987, I wish to thank Dr. H. Bush for almost seven years of leadership as the Director of the London Centre, and Miss M. Bolster who will be retiring from the Kingston Regional Cancer Centre after almost 40 years of service -- a remarkable record.

As good as the staff are, to function they need facilities, equipment and operating funds. 1986 saw major changes in funding particularly for capital needs.

In 1986, the Government made major commitments for "bricks and mortar" to rebuild the Princess Margaret Hospital (PMH), the Regional Cancer Centres in Hamilton and London, and to build a new Centre in Sudbury.

In London, construction is under way at the Westminster Campus with a planned opening in 1988. In Sudbury, plans are approaching their final form with the aim of beginning construction in 1987 and completing it in 1989. In Hamilton, planning is actively proceeding for a new Centre in continued association with the Henderson General Hospital. Further, permission was given to begin planning for both the Civic and General Divisions of the Ottawa Regional Cancer Centre. Also it became evident in 1986 that, in addition to rebuilding the PMH, central Ontario would need more facilities to meet the anticipated treatment requirements of increasing numbers of cancer patients. These enlarged capital needs can be met only through success in the $50 million capital campaign (to which the Chairman has referred), and additional funding from Government beyond what has been committed to date.

In addition to space, expensive equipment is required. It is a pleasure to record the commissioning, during 1986, of a linear accelerator in the Thunder Bay Regional Cancer Centre and the delivery of a linear accelerator to a newly constructed bunker in the Windsor Regional Cancer Centre.

From time to time, new programs must be introduced to fulfill our mandate under the Cancer Act. Notable advances in 1986 included further development of the Northeastern Ontario Oncology Program in Sudbury, the extension of our affiliation with physicians and hospitals in the communities particularly in the

Hamilton region, and the extension of the Cancer Information Service, jointly funded with the Canadian Cancer Society Ontario Division.

The Foundation has undertaken a notable new venture in the field of prevention. In concert with the Addiction Research Foundation, Ontario Cancer Society Ontario Division, Heart and Stroke Foundation of Ontario, Ontario Lung Association, and Ontario Mental Health Foundation, we have recommended to the Minister of Education "that the Ontario Ministry of Education makes the teaching of prevention of smoking as a major health issue compulsory within the health education core curriculum, commencing at the primary level and continuing throughout the entire school program". We have had a most encouraging response from many school boards, principals and teachers' associations. Some of our staff have undertaken or are actively planning research into cancer prevention by chemical means (chemoprevention) or dietary change. Our Research Advisory Panel has brought forward plans for a major research program in prevention which we hope will be launched in 1987. Plans have been developed for programs in "secondary" prevention, namely early detection or screening which we aim to have in operation in 1987.

In 1986 it became apparent that our expanded programs required major reorganization to permit our Centres more operational autonomy within a system of programmatic and fiscal accountability. We have taken steps to strengthen administration and accounting at the Centres, and to delegate some program elements (e.g. information-computer expertise) to the Centres. We are now in the process of reorganizing and strengthening Head Office so that it may respond adequately to the Centres, to improve human resource functions, internal audit, and to establish meaningful planning and health economics functions.

We believe that the Foundation's network of Centres and its Province-wide programs (e.g. Ontario Cancer Registry) brings to the citizens of Ontario a world-class cancer control program. To continue this program we need the continuing support of the people of Ontario and their Government, to whom we are grateful.

J. William Meakin, M.D.,C.M., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the Head Office of the Foundation.

"BEYOND BRICKS AND MORTAR": A CITIZEN'S VIEW OF CANCER CONTROL IN ONTARIO

GORDON BAGLEY*

Cancer physicians and scientists are worried. Cancer care for the people of Ontario is in a state of crisis. It isn't easy to dedicate your life to the care of people, many of them desperately ill, and then have to look on helplessly while the system that has been built up over the past 40 years seems to be slipping away.

It is difficult when those whose lives are threatened come to you for help to tell them that they must wait up to a month for therapy; to ask them to wait in a crowded corridor, sometimes late into the night for a turn on equipment that is often outdated and overworked. However, this is the reality at some of Ontario's regional cancer treatment centres. What's worse, conditions will steadily deteriorate unless legislators and the people of this province are informed immediately about the true cost of cancer control.

Mark Twain once wrote "each person is born to one possession which outvalues all his others – his last breath". But each year that last breath becomes increasingly expensive for Ontario's cancer patients.

It is a situation that calls for a new order of priority among our legislators and the public who, through taxes and donations, fund the eight regional cancer centres that make up the Ontario Cancer Treatment and Research Foundation and the Ontario Cancer Institute incorporating the Princess Margaret Hospital.

Everyone in this province – from the premier to the person who washes his car – has a stake in our cancer control system and everyone should realize an effective system goes far beyond bricks, mortar and equipment. It's one thing to build a house, but quite another to operate and maintain that house over the years.

Since the early 1980s, the doctors, scientists and administrators who look after Ontario's cancer control system have known that the facilities and equipment were exhausted.

Fortunately the Ontario Ministry of Health responded and in August of last year set aside $200 million (contingent on the Foundation raising $50 million through private-sector donations) to rebuild the Princess Margaret Hospital and enhance regional cancer centres in Hamilton, London and Sudbury.

Still, as timely as the Ministry's commitment was, the $200 million does not cover the pressing problem of operating costs – those expenses beyond "bricks and mortar". These have steadily increased over the past 10 years to the point where cancer care in this province is threatened – not just for want of equipment and space, but beyond that, for want of the funds to properly operate and maintain even the present system.

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*Freelance writer interested in science and public health issues

Linear accelerators, used in radiation therapy for instance, not only cost $1.5 million each to install, they require several hundred thousand dollars a year to maintain and operate. Thanks to a regionalized cancer delivery system, these machines are dispersed efficiently throughout Ontario to reach the maximum number of patients at the minimum cost. However, the burden of operating and maintaining them is not static and increases year after year in step with technical and therapeutic advances in the field of nuclear medicine.

Similarly, chemotherapy costs associated with the new anticancer drugs used by Ontario's regional cancer centres have escalated at the time when their increasing effectiveness is saving more lives. Chemotherapy treatments alone cost the Ontario cancer control system $4,478,000 annually.

These and other expenses related to training, staffing and research activities have left the OCTRF and OCI/PMH operating in the red by an estimated $10 million per year.

In fact, it is the chronic shortfall of operating revenues combined with the "bricks and mortar" issues that have the cancer doctors and scientists of Ontario so apprehensive about the future of cancer care in this province, in the face of a steadily aging population and a steady increase in the number of cases.

Right now, cancer is the second most common cause of death in Ontario after cardiovascular disease, but even that alarming statistic underplays the tragedy, because cardiovascular disease usually affects people in the fourth, fifth and sixth decades of life. The ability of cancer to strike at children and teenagers makes it a much deadlier foe than cardiovascular disease in terms of the potential years of life lost.

Comprised of a 100 different diseases, each with their own characteristics, cancer is an enemy that must be battled by many people on many fronts. It is an expensive, escalating, high-tech battle of the nuclear and chemical age and over the next 20 years the fighting is going to get heavier and more expensive.

Why? Because Canadians, as a people, are healthier than ever before. As a result, we live longer. Cancer is most often a disease of old age.

Although the enemy has been rolled back and put to rout on a number of fronts, no "magic bullet" is yet in sight. So the disease remains pervasive. Between 1974 and 1984, the number of patients needing treatment for cancer increased by 37%. By 1994, it is estimated the number of cases will rise a further 47%, even though the population is expected to grow by only 12%.

In short, one in four Ontarians will develop some form of cancer before they reach age 74.

Given the massive threat of cancer to Ontario's people, each citizen must rally to the support of one of the best cancer control programs in the world. Its leaders –

many of them world-class researchers and clinicians – have warned for years that without sustained and continuing support from government, corporations and private citizens, the entire system of cancer control is in grave danger.

The individual citizen wants to be assured that the system he may one day rely on to save his life is ready for an impending avalanche of cancer.

Further, the leaders of Ontario's oncological community warn of a tragedy in the making unless the community provides not only capital investment and operating funds but also money to recruit, supply and expand the "critical mass" of cancer specialists and their support staff.

To stay at the forefront of cancer medicine and meet its commitment to Ontarians, this province's cancer control system requires the support of a people and government who accept the magnitude of cancer's growing burden and are willing to give this fearsome disease a high financial priority.

Without a rapid updating of the cancer control system within a decade, the sheer number of patients needing care will overwhelm the resources of the OCTRF and the OCI/PMH. In that eventuality, quality of care must decline, not because the scientists, doctors, nurses, technicians and others fighting the disease have lost interest, but because they won't have the manpower, tools or the space to carry on.

OUR PAST

In June 1931, a Royal Commission – known as the Cody Commission after its chairman, Henry John Cody – was set up by the government to make recommendations concerning the use of x-rays and radium in cancer treatment. As a result of their studies and deliberations, they produced a comprehensive picture of the world's cancer establishments and devised a system for cancer control that continues to this day.

In response to the recommendations of the Cody Commission, the province entered into an agreement with selected hospitals throughout Ontario: a covenant that called for the formation of a network of regional cancer treatment clinics, research laboratories, creation of a cancer institute and a public awareness program to help Ontarians inform themselves about the disease.

That agreement took 12 years to come to fruition, being held in abeyance from 1939 to 1945, as Canada and her allies were drawn into the global conflict of the Second World War.

In those six years, 41,992 Canadians died in defence of freedom. A lesser known statistic, but every bit as tragic, is that by the time the last bullet was fired in anger, 80,000 Canadians had died of cancer. As a nation, we had poured $19 billion into the war effort and, in the same period, we had spent just $5 million to fight cancer.

Provincial legislation was passed on June 13, 1943 to create the Ontario Cancer Treatment and Research Foundation but little could be done to put the Act into effect until 1946.

Even then, the "program of diagnosis, treatment and research in cancer", which the legislation called for, got underway only because the Foundation's new directors had spent the previous three years raising public funds to upgrade existing cancer clinics in a selected number of hospitals and communities across Ontario.

The first cancer clinic opened in a new wing of the Kingston General Hospital in March 1947. Equipped and staffed by the Foundation, it became the model for six other treatment centres which still exist in Hamilton, London, Ottawa, Thunder Bay, Toronto and Windsor.

In concept, these seven regional cancer centres represented a new experiment in medical organization. By combining research at the university level with clinical diagnosis and treatment – first by radiation and later by chemotherapy – the Foundation was able to unite into a common front the scientists, doctors and medical disciplines concerned with cancer.

Information from research was made available quickly to clinicians; advances in the laboratory were cross-checked against advances in therapy; patients were reassured that oncologists in the various specialties met together regularly to discuss each individual's case and determine how it might best be handled.

Instead of the helter-skelter approach of private interests and isolated institutions, which is the hallmark of cancer care in the United States, the Foundation provided a common focus through which the "best of the best" could come together to share information in their common search for improved care.

Since its inception, the Foundation has associated itself with researchers at the major universities in Ontario. As early as 1945, research grants were awarded to investigators at several of these institutions.

The accomplishments of Ontario's research scientists probably are better known to the world than to the average Canadian. For instance, a grant from the OCTRF helped Prof. E.F. Burton perfect the world's first electron microscope – an advance that permits researchers to look into the very genes of a human cell, to explore the way viruses "hijack" living organisms and to search for the biological mechanisms of cancer cells that might be "turned off" or destroyed.

The OCTRF also helped Dr. Raymond Parker and Marian Chapman of the University of Toronto in their study of mouse tumors in eggs and in tissue culture. While working on this project, Dr. Parker developed the tissue culture Dr. Jonas Salk later used in the development of the Salk vaccine – a medical advance that helped to remove the threat of poliomyelitis epidemics in our time.

Further, Prof. Charles Best, co-discoverer of insulin with Dr. Frederick Banting, was funded by the Foundation.

Dr. Ivan Smith, Director of the London Regional Cancer Centre, was the first to treat a cancer patient with a cobalt-60 radiation beam unit – the "cobalt bomb".

The list goes on. Ontario researchers funded by the OCTRF explained "staging" – a key concept in modern management and control of Hodgkin's disease; others supported by the Foundation helped develop agents used in chemotherapy; the cell "models" now used throughout the world to study how cancer cells grow were developed by OCTRF-funded researchers. Others conceived and performed experiments, which have contributed to a greater understanding of the human blood system and, eventually, how bone marrow transplants could be used to combat certain forms of leukemia.

Today, OCTRF researchers use CT scanners to outline tumors and ultrasound to diagnose cancer of the breast without risk to the patient; they continue to experiment and study and explore.

Augmenting this sustained effort in cancer control was the opening in 1958 of the Ontario Cancer Institute incorporating the Princess Margaret Hospital – an independent organization with a wide range of radiotherapeutic equipment and associated technology. Named after Her Royal Highness, the Princess Margaret Hospital was opened during her visit to Canada in May 1958. It had 87 beds for cancer patients and two floors dedicated to research.

Over the next two decades and into the 1980s, the two organizations (the OCTRF and the OCI/PMH) have strengthened their bonds with the general hospitals that host the regional cancer centres. They have pushed for and funded outreach programs, interhospital programs, research and education programs and have worked in collaboration with and support of many agencies notably the National Cancer Institute of Canada, the Medical Research Council of Canada, and the Canadian Cancer Society Ontario Division.

Like cancer control organizations all over the world, the OCTRF and the OCI/PMH realize the march to victory over cancer is a journey of many experimental steps, each small success building on the successes that have preceded it. Cancer is not yet beaten, but it can be. Progress has been made.

OUR FUTURE

Today, cancer does not come into the lives of individuals and families in Ontario to wreak havoc unopposed. In fact, modern care has reduced the death rates due to cancers such as leukemia, Hodgkin's disease and cancer of the testicle. Death rates due to breast and intestinal cancer have stabilized and those due to cancer of the uterus and stomach have declined.

Unfortunately, deaths due to lung cancer continue to increase sharply for both sexes and will continue to do so until public attitudes toward cigarette smoking force a general social response to this deadly habit.

The cancer control system must not be left to decline and possibly disappear due to a lack of operating funds. Many believe that if such a thing happened, Ontarians would inherit a fragmented treatment and research system in which hospitals and communities would, by default, demand government money to pursue private cancer programs. The result – an expensive "free market" cancer treatment program – would lack the co-ordinated structure, the quality control, and the effectiveness gradually achieved by the Foundation over these past 40 years.

The better alternative, is a decision by the people of Ontario to go above and beyond the recent $200 million commitment to "bricks and mortar".

In short, Ontario's cancer control system urgently requires continuous and adequate operational support to offset inflation and to keep up with the steady increase in the cost of technology and drugs.

It needs cash to re-establish, expand or develop fundamental treatment programs within the regional cancer centres – such things as proper psychosocial support and palliative care programs for patients trying to deal with the shock of having cancer, the stress of therapy or the realization they will not recover from the disease.

Better communication systems are needed so that regional cancer centres can "network" with local physicians and specialists in the communities where cancer patients live – an outreach program so that the sick and dying don't "slip through the cracks in the system", so their medical records aren't lost and so they and their families continue to have the proper medical support after they have concluded primary radiation and chemotherapy.

On the clinical level, operational support is needed to establish and develop much needed dental oncology units on a regional basis, to treat patients who require reconstructive maxillofacial surgery following cancer surgery and radiation.

Additional funding is required so dentists who choose to specialize in this field can be adequately renumerated; cash also is urgently needed to recruit students in the chronically understaffed fields of radiotherapy, radiation technology and medical physics; support is needed too, for the upgrading of training programs and teaching facilities in those three disciplines because standards of education must keep pace with the latest breakthroughs and techniques.

Furthermore, as the incidence of cancer among the citizens of Ontario continues to increase towards the mid 1990s, operating costs will likewise increase as the Foundation hires more doctors, nurses and support staff to handle the burgeoning caseload.

On the research level, the Foundation needs funding for everything from laboratory research to molecular biological experiments and clinical trials – the flashpoint at which physicians hope "breakthroughs under the microscope" will translate into the improved treatments.

Funds are also needed to inaugurate cancer prevention – programs which are expected to be one of the most rapidly growing phases of research over the next decade. Beyond mere talk about prevention, its achievement requires the cash to enable scientists and doctors to investigate, for instance, methods of behaviour modification that would help people quit, resist or never start smoking tobacco. Also scientists are looking at chemoprevention techniques – methods of interfering with the pathogenesis of cancer so smokers who just can't or won't quit can still be protected.

These and other primary "preventive" techniques are now approaching the clinical trial stage – assuming funds can be obtained to bring these laboratory advances into the public domain.

Secondary prevention or early diagnosis, which has always been a major part of the Foundation's mandate, also needs an operating budget. For instance, screening techniques are available at regional cancer centres that detect and act against breast and cervical cancers before they become too entrenched to destroy, however, the Foundation needs operating funds to make sure that every woman who should take advantage of these screening programs is aware they exist.

All these operational initiatives are important if this province is going to stem the tide of cancer that will be inexorably rising as we head into the 1990s. Where does the money to meet the ongoing expenses come from?

Last year, the Ontario Ministry of Health sent a clear message – in the form of a large capital grant – that it recognizes the need for this province's cancer control system. With the help of donations from corporations and private individuals, that money will ensure the bricks and mortar are laid. The "house" that Cody and previous Ontario governments built will be refurbished, replete with much needed additions and alterations. What is needed now, is for government and the people of this province to understand the fragile state of our present program and the massive challenge before us.

The doctors, scientists, nurses, administrators and support staff that make up the cancer control system in this province believe that, given the facts, the government and the people of Ontario will recognize that the rising incidence of cancer is a real and present danger. We must act now. They ask only for sufficient operational support to do their job – protecting the one in four of us whose life will be threatened by cancer within the next 10 years.

To illustrate the current needs of the cancer care system, the editors of *Cancer in Ontario* invited the directors of the eight regional cancer centres to summarize their current state of preparedness for the expected rise in cancer incidence in Ontario. These summaries now follow:

HAMILTON

The Hamilton Regional Cancer Centre (HRCC), the designated tertiary care facility, serves the Central West Region of Ontario and its population of 1.7 million. The philosophy and goals of the HRCC reflect the challenges we face as an established regional cancer centre of the OCTRF. The central goals as enunciated by the directors of the regional cancer centres in 1984 are: "To reduce the morbidity and mortality from cancer in the Province of Ontario through the mechanism of the development of a centre of excellence in relation to service, education and research". To realize these goals, the HRCC is pursuing three interconnected objectives: the delivery of optimal patient care; the pursuit of excellence in teaching; and the pursuit of excellence in research.

The broad scope of activities at the Hamilton Centre includes radiotherapy, chemotherapy and multidisciplinary care. Clinical and laboratory research are strongly emphasized and, in addition, we have instituted a comprehensive psychosocial support program both in the Centre and on the oncology wards of the Henderson General Hospital. In addition, the Centre co-ordinates or collaborates in nine outreach clinics, which enable patients to receive chemotherapy and follow-up care closer to their homes.

The Hamilton Centre, when it moved to its current site in 1965, was designed to meet the burden of cancer care at that time. Its design and size could not take into account the need for an extensive chemotherapy program, new technologies, extensive research program, multidisciplinary care, professional education responsibilities and the increase in cancer incidence. Since 1965, a major explosion has taken place in basic biological and clinical knowledge, which made necessary major expansion in staff and space. Although the ensuing years saw a number of minor renovations and expansions, the HRCC is experiencing a considerable shortfall and the requirements for staff and space to meet the projections of growth will greatly accentuate this shortfall. It is essential to meet the need for new programs with appropriate staff and equipment if we are to achieve our fundamental goal as a "centre of excellence" in cancer care.

One might demonstrate the existing shortfall at the Hamilton Centre in several ways. The number of non-skin cancers registered at the Centre more than doubled between 1968 and 1983 (992 to 2190). It is predicted this number will double again in the next 15 years. Our current space limitations are clearly demonstrated by "square feet per treatment visit". In this respect, the Hamilton Centre is far below the other centres, except for London Centre; in size relative to service load, other centres have 2.5 to 6 times the number of square feet per treatment visit.

Space limitations impose serious limitations on the Centre's functioning including:

- increased waiting times for patient appointments;

- limited time available during visits because the room is needed for the next patient;
- limited space available in waiting rooms;
- reduced follow-up visits to the point where we have the highest ratio in the Province of active treatment to follow-up visits;
- increased waiting time (up to three weeks) for radiation therapy;
- full use of chemotherapy resources making necessary establishment of outreach clinics;
- severe constraint of research programs and fragmentation of laboratory research to three areas – at the Centre, the adjacent Henderson General Hospital, and McMaster University;
- serious curtailment of student placements at the Centre, which restricts our ability to fulfill our obligations to nursing and medical education; and
- insufficient space to accommodate additional funded staff, including physicians and secretaries, who are needed to meet the current patient caseload. This has made necessary a retreat to trailers in the parking lot.

The Ministry of Health's grant to the HRCC will provide approximately two-thirds of the funding necessary to build a new facility which will enable the Centre to continue to strive for its goals of excellence in service, education and research. In addition to the need for extra funding and for the facility itself, we need continuous financial and other support to deal with a steadily increasing patient load, and we need to acquire and master the new technologies and modes of treatment required for this greatly increased patient load.

Also it is essential to provide ongoing funding for the expansion of existing programs such as chemotherapy, radiation therapy, psychosocial support and patient education if the Centre is to provide optimal patient care.

If newer, more effective treatments are to be identified with scientific precision and patients are to be guaranteed the best "standard" treatment, continuation and expansion of support for both basic laboratory and clinical research is critical. It is also essential if we are to attract to the Centre first-class clinicians and scientists.

In addition, continued funding must be found for education if the Centre is to provide educational resources in oncology to accredited medical and nursing schools, as well as participate in postgraduate training programs. Education in oncology is essential to both optimum patient care and future cancer research.

Funding must also be available for the development of new programs and the acquisition of new technologies to ensure the delivery of optimal patient care.

Although construction of a new facility will allow the Centre to achieve a number of its goals, the need for ongoing funding for programs cannot be over emphasized if the Hamilton Regional Cancer Centre is to achieve its goal as a centre of excellence.

W.M. Hryniuk, M.D.
Director

KINGSTON

In 1977, the Kingston Regional Cancer Centre moved into spacious new quarters. "Expansion space" was included in the design. This has now been occupied. We are not unduly cramped, but prudence demands that we start planning for increased space requirements for the 1990s. Radiotherapy equipment is pivotal to a cancer centre. Our simulator is virtually beyond repair and our cobalt unit needs urgent replacement.

These are the "bricks and mortar" items, and while they are clearly crucial to the care of the patient with malignant disease, such care, if it is to be outstanding, requires far more. In addition, to be just "good enough" is not good enough. The goal must be to be superb. We owe this to the patients who come to us with their malignancies, their plights and their fears.

High quality medical, nursing and technical care is essential. This requires not only that the training of the personnel be superb, but also that the level of expertise be maintained and developed through continuing education programs. This in turn demands adequate funding for travel to appropriate conventions and courses for staff–not a luxury but an essential. It demands adequate funding for library facilities, for guest lecturers, and for education in all its various guises.

Superb clinical care demands that treatment policies be carefully defined, based on the best available evidence, and that the effectiveness of defined policies be carefully audited and monitored. This too requires adequate funding. Computer hardware provides the means, but this will be wasted in the absence of trained clerical personnel working in close collaboration with physicians and dedicated to the abstraction, collating and analysis of patient-related data. In this regard, we, in Kingston, are exploring the increased use of the OCTRF central computer, on a pilot basis and will also investigate, on a research basis, the value of a dedicated analyst in evaluating our data relevant to breast cancer. We do not believe that this essential component of medical care can be absorbed by our current clerical staff and envisage increasing staffing needs in these areas over the coming years. We must be able to compare the quality of the care that we provide, in so far as it can be measured by "survival curves", incidence of toxicity, and, yes, cost-effectiveness, with "best in the world" data, so that we can correct deficiencies where they are detected.

While an integral component of quality care related to the provision of outstanding radiotherapy and chemotherapy, we dare not exclude from this the supportive care that is so important to the patients and families with these dread diseases. At the very least, good supportive care relates to the speed with which patients are seen in consultation, to the warmth, compassion and accommodation they experience when making appointments, when communicating with clinic staff, and when attending the centre. It relates to the delays patients experience in waiting rooms and in "getting onto the machines". It relates to the attention paid to symptom control, and to environmental and work-related problems. And at another level it relates to the expertise available in reducing the anxiety associated with these illnesses. This is a major area for research which we, like others, are undertaking and it will require funding – both for the research and for the implementation of the policies which should follow such research. We do not yet know the value of group or individual psychotherapy, of behaviour modification techniques, of having a psychiatrist or a psychologist on staff, but if some or all the approaches that are being investigated prove valuable, they will certainly require additional funding – money that will be well spent indeed!

Staff morale is key to patient care. Obviously this has many components, not the least of which are salary, and the support provided by administration in an individual centre. It does, however, require that workloads be appropriate – neither too demanding nor too slack. Standards will need to be defined, and this is a worthy area for research that can well be undertaken with the collaboration of business schools, and, indeed, business itself. This too will require funding. Once standards are established then they should be met even if this adds expense.

Research too is an essential and not a luxury. It provides the intellectual basis for a vibrant and alert clinical faculty and provides the infrastructure for the care of future patients. We are fortunate to have a cadre of superb basic-scientists and clinician-scientists in the Kingston Centre. Their work MUST be supported.

We pride ourselves on the quality of the educational programs in our department. This is the consequence of dedicated effort from many faculty, and this in turn needs recognition, nurturing and support.

Our goal is excellence – excellence of technical care; humane, concerned and personalized supportive care of the highest order; excellence in our research programs, and excellence in our teaching programs; all in an environment of high staff morale; and all against a background of fiscal responsiblity and an awareness of the need for cost-effectiveness. We will willingly pursue this goal. We need moral support; we need the recognition that what we are pursuing is worthwhile; we need financial support; and we need the security that such recognition and support will bring.

A. David Ginsburg, M.D.
Director

LONDON

During the last few years, the London Regional Cancer Centre has progressed rapidly and has evolved new programs in cancer management. Centre activity has shifted from a predominantly radiotherapy service-oriented base to an expanded program in medical oncology, new commitments to experimental oncology, psychosocial support, palliative care and a more focussed definition of the primary-care role for nursing oncology. The greater emphasis on care (as opposed to cure) reflects a realistic appraisal of cancer treatment in the 1980s. While all hope that new advances in basic and clinical research will lead to reduced suffering and possibly eradication of cancer, this is unlikely to occur in the near future. Therefore, we have recognized the necessity to increase our commitment to psychosocial support and palliative care using the skills of social workers, nursing oncologists and physicians. We will need to continue to strengthen these areas and provide a facilitatory role for community-based, health-care services.

During recent years a strong commitment has been made to multidisciplinary patient care incorporating radiation, medical, gynecologic and surgical oncology in particular. Therapeutic issues are likely to become even more complex and better interfaces for group decision-making such as tumor boards will continue to evolve. At a centre level, within the OCTRF, we will need to maintain special strengths in radiation and medical oncology and to provide, within the centre, an environment which welcomes the participation of other specialties, such as gynecologic and surgical oncology.

During the past five years, there has been an exponential increase in the number of experimental oncologists at the London Regional Cancer Centre. Our relocation to the new centre will provide a significantly increased laboratory space and it will be important to encourage high standards of basic research within this facility. Regional cancer centres are uniquely placed to provide the clinical interface for research emanating from the laboratory. In future years such activity will be actively encouraged at the London Regional Cancer Centre.

Historically, most of the major diseases during the last century have been eradicated through prevention: cancer may prove to be no different. We are committed to a cancer control program in Southwestern Ontario and already have undertaken applied clinical research in the area of analytical dietary intervention. We need to set policy guidelines for screening and, in the near future, will increase our profile in this area. Once again, we should play a leadership and facilitatory role in cancer screening and interface more directly with the health-care facilities in the region, including the Canadian Cancer Society. Also we are poised to undertake a major public education program, which may provide a unique opportunity to work in tandem with the Canadian Cancer Society. During the next 15 years, cancer incidence is expected to increase by 50% and it has been estimated that cancer prevention can reduce its incidence by the same percentage. Therefore we will need to mount a vigorous cancer control program and commit appropriate resources to this extremely important area.

The London Centre represents a microcosm of the Ontario cancer system. It would be futile to concentrate on fragments of the cancer problem and hence we will need to adopt a more holistic approach if we are to achieve comprehensive cancer control. Such control includes prevention and early diagnosis, basic research, cure where possible, care and education. In the immediate future, cancer incidence will continue to increase and the onus is on us to provide a rational cancer service which will reduce the impact of this disease on the population we serve.

L. Levin, M.B.,Ch.B.,F.R.C.P.(C)
Director-Elect

OTTAWA

The Ottawa Regional Cancer Centre is composed of the Civic and General Divisions.

The Civic Division moved into a new building in February 1978 designed to provide for 2000 new cancer cases a year. This number was exceeded in 1986 leading to a lengthening waiting list for both initial consultation and the subsequent time slot on the radiation treatment machines or in the chemotherapy day-care area. Over the nine years, the administration has made many attempts to increase efficiency by remodelling to increase the number of examining rooms and offices.

Each time, however, an annual increase in new patients of between 5% and 8% has rapidly swamped the improved facilities. Today no further worthwhile renovation is possible and the only solution is to enlarge the building by three floors. The present staff is overloaded and frequently manifest signs of stress and burn-out.

The General Division opened in the new General Hospital in August 1980. Within five years the number of new patients had reached the designed capacity. During its short existence, 21 separate minor remodellings have been necessary to permit the Centre to function adequately. As at the Civic Division, no further worthwhile renovation is possible and the only solution is to expand out and up for three floors to add about 76,000 gross square feet of floor space.

Seven years ago, we built a bunker for a high-energy linear accelerator, which fortunately should be in place by the end of this year.

Medical physics play a crucial role in the safe and quality-assured practice of radiotherapy. In addition, medical physics play a central role in the development of new cancer therapy techniques through developmental research. The Department of Medical Physics consists of a multidisciplinary team of physicists, dosimetrists, electronic technicians, computer programers and machinists. This team supports all operations of the Centre.

At the present time, the Department of Medical Physics is severely understaffed and thus cannot provide an adequate support service to the Centre. For example, because of a shortage of physicists we cannot do regular calibrations on radiotherapy devices and we do not have staff time for development of new treatment techniques. A shortage of electronic and machine shop staff allows too little time for regular preventive maintenance on the radiotherapy machines and consequently increases the number of breakdowns. Also a shortage in dosimetry staff prevents adequate treatment planning and dose measurements for radiotherapy.

Radiotherapy is strongly dependent on equipment and on high technology and thus it is essential to replace and upgrade worn-out and outdated equipment. In this area a shortage of technical support and of radiotherapy machines forces us into 12-hour treatment days. In addition, the equipment is growing old and is becoming unreliable.

In essence our situation in late 1986 is characterized by a shortage of space, a shortage of all types of specialized medical and support staff, a shortage of radiation treatment machines, a shortage of chemotherapy day-care facilities, and inability to freely introduce new programs and techniques to improve the treatment of cancer. All of this reflects insufficient funding over 10 years; our grants have only kept pace with the increase in the cost of living at a time when the patient load has increased at least 5% each year compounded, and treatment techniques have become much more complex.

That the standard of patient care has been maintained in the face of such daily frustrations is due entirely to the dedication and devotion of all the staff members.

As at all the regional cancer centres of the OCTRF, our goal is world-class excellence, not only in technical skills and research but also in the compassionate care of the individual patient, with particular attention to the psychosocial needs of both patients and their families. To do this we need consistent, regular support from the government, and from charitable, corporate and private donors.

G.E. Catton, M.B.,B.S., D.M.R.T., F.R.C.P.(C)
Director

SUDBURY

On August 5, 1986, the Minister of Health, the Honorable Murray Elston, committed $20 million for the construction of a comprehensive cancer treatment centre in Sudbury and for additional 36 new cancer treatment beds (bringing the total to 58) at the Laurentian Hospital. The centre will provide comprehensive cancer treatment services in Sudbury and will serve the people of Northeastern Ontario.

We anticipate that the new centre will have a workload of approximately 1650 new cases by 1991, 1951 new cases by 1996, and 2274 by 2001; this is based on a somewhat low assessment of referral rate of 51.5%. The new centre will have comprehensive treatment facilities and, at its opening, will be equipped with superficial and cobalt machines, two high-energy linear accelerators, and a simulator. Also there will be a tumor registry and research laboratories. The centre will be 4972.5 departmental gross square meters (DGSM) and the functioning program estimates a staffing requirements of 117.5 full-time equivalents.

The centre will be supported by Laurentian Hospital, the host institution, which will provide diagnostic and inpatient services including, at the opening of the centre, an additional 36 oncology beds. Dedicated oncology bed requirements are anticipated to be in 1991 – 45, in 1996 – 57, and in 2001 – 70, with overall totals of non-surgical oncology beds in 1991 – 67, in 1996 – 79, and in 2001 – 92.

In addition, the Canadian Cancer Society will build a lodge with 35 rooms (70 beds) for out-of-town patients and their relatives on the same site as the centre. Apart from the beds, the functional program for the hospital (submitted in April 1986) has not been approved. Also we await approval for a CAT scanner for the centre and the Laurentian Hospital. The only (offsite) CAT scanner in Sudbury has a three-month waiting interval for elective scanning and hence is not likely to be available for treatment planning for radiation therapy.

The completion of the new centre is scheduled for 1989. Currently, the architects are completing the sketch plans for presentation, with the preconstruction budget, for Ministry approval in early 1987, before proceeding to the final working drawings. The process has been delayed by long waits for the Ministry approval, February to August for approval of the functional program, and April to December for the block schematics, and currently the process is six months behind schedule. Presently the Northeastern Ontario Oncology Program (NEOOP or the "Program") and the Laurentian Hospital co-chair the working group for the new centre and hope to get back on track in 1987. The preconstruction budget, as defined in the functional program, has not been accepted by the Ministry. It is considered to be excessively high, particularly with regard to staffing levels, whereas it does not adequately budget for the regional elements of the centre. Also it is conservative in the assessment of medical manpower, and the new patient referral rate (51.5%) and subsequently on the projected case load figures. The functional program does not include operational programming for laboratory research.

In 1987 it is planned to improve the clinical services and to begin an outreach program, to network across the region in collaboration with the existing programs from the Princess Margaret Hospital. Recruitment has started for a chairman of radiation oncology to develop the radiation department at the new centre. Two radiation residents, funded by the Program, are in training for Sudbury at the Ottawa Regional Cancer Centre and in 1986 the program recruited and funded two medical oncology residents for future service in the North East. They are training in Ottawa and will rotate to Sudbury during their residency period. It is hoped to achieve affiliation with a major health science centre in the new year.

1987 will be a challenging year for the Program. It will require a maximal effort from all staff and adequate fiscal resources to achieve the goal of fully developed comprehensive and integrated programs, with the necessary human resources, to establish a centre of excellence, with proper regional programs and networking for cancer treatment, research, education and prevention for the North East.

R.E.T. Corringham, M.B.,B.S.
Director

THUNDER BAY

When, in 1978, our staff moved into a new clinic building from the crammed quarters in Port Arthur General Hospital, we felt very comfortable. At that time, however, hardly any chemotherapy was done in the Centre and we had two physicians and about two dozen staff members. Since that time, our number of new cases increased by 50% and treatments became considerably more complex and demanding. Our staff number almost doubled. No reserve space was included in the design of the clinic, so it is not surprising that, at this moment, our Centre building is crammed with people and equipment. We had to move some offices into the lodge and rent again some rooms from Port Arthur General Hospital. Planning for increased space is a matter of high priority right now. We anticipate that any addition to the Centre will have to increase the floor area by at least 50% but if new programs, which the Foundation is now considering, i.e. prevention, screening, early detection and education, should be provided for, an even larger space would be needed.

While we proceed with planning for the expansion, we have to be aware of a new development in the community. Three acute care hospitals are negotiating a corporate merger as a preliminary stage for possible construction of one 800-bed central hospital. Once this is in operation, our host hospital likely would become a chronic-care institution and we would need a new cancer centre adjacent to the new acute-care hospital. From this, it is quite obvious that, over the next 10 years, considerable amounts of funding will be required for "bricks and mortar" in Thunder Bay.

Buildings and equipment, however, do not guarantee a high-quality program for cancer control. In the last few years we have submitted proposals for funding of several new programs, such as a chemotherapy outreach program at Fort Francis, but did not obtain the necessary support. We have responsiblity for a drainage area in Northwestern Ontario which is as large as the areas covered by the other seven regional cancer centres but it is sparsely populated. To improve the service, we have to be able to arrange for patients to get at least some of their treatment, like chemotherapy, closer to their homes. One step towards this goal is a chemotherapy outreach program such as that we have agreed on with La Verendrye General Hospital in Fort Frances. Program details have been worked out and some patients are being treated as if this program already was in place and some staff training has been done. However to do it properly, we need special funding for training of staff at Fort Francis, proper supervision, telephone and computer connections and continuing education. If this program is successful, the Thunder Bay Centre will probably be asked to provide similar services to communities east and west of our city.

Demands for continuing education and training are difficult to meet at this time. Our library is the only one in Northwestern Ontario with a special interest in oncology; thus we subscribe to some 35 periodicals and purchase yearly a considerable number of books. However, we have not been able to acquire support for a part-time professional librarian, needed to establish this library on a firm basis and develop the system so we could open the library to local students, physicians and nurses. Our Centre has academic affiliation with McMaster University and to fulfill this role our staff needs to participate in Hamilton-based programs. Again this requires frequent travelling. Thunder Bay is a relatively isolated city without a medical school; thus for further education and maintenance of skills, our physicians, nurses, physicists and technologists have to travel outside the area. This in turn demands adequate funding for travel and also to allow us to invite guest speakers and visiting clinicians.

To provide the best possible care, it is important to maintain a high technological standard of treatment. As part of this effort, we recently acquired a new linear accelerator. However, we are aware that other non-technological aspects of cancer care are just as important. For example, psychosocial support has considerable potential to improve patient comfort and well-being and also to contribute to research effort. We believe that, with the support of the Department of Psychology of Lakehead University, we have an opportunity to do significant research and to provide a valuable service. For this purpose, we would like to add to our staff a clinical psychologist who would have a cross appointment at Lakehead University. We are looking for funding for this program.

While we do not expect to develop laboratory research as part of our Centre's program, we have a good opportunity for clinical research, particularly through participation in clinical trials. We need to establish a clinical research unit, supervised by an experienced nurse oncologist. This would represent "an add on" to our current nursing capacity. We have obtained a grant from the Port Arthur Rotary Club of $10,000 specifically for this purpose. We would hire such a person immediately; however further budget support will be required until adequate income is assured from Canadian and U.S. National Cancer Institutes' grants.

During the last few years, the Foundation and its Thunder Bay Centre have operated under considerable financial restraints in spite of increasing number of cancer patients and increasing complexity of modern therapy. Further, there is growing awareness of the need to develop new programs to implement cancer control by increased involvement in research, education and prevention of cancer. Moral and financial support from our own community encourages us, however, to make sure that at all times the care for our patients here is second to none, we will need the support of the people elsewhere in Ontario.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

TORONTO-BAYVIEW

The Toronto-Bayview Regional Cancer Centre (T-BRCC) provides multidisciplinary cancer consultation, assessment and treatment services to ambulatory patients. The T-BRCC presently has 12 consultation and assessment rooms in its outpatient area. There are four high-energy radiotherapy treatment machines (three linear accelerators and one cobalt unit) in the Centre, and one planning simulator to support patients on radiotherapy treatment.

The T-BRCC and Sunnybrook Medical Centre (SMC) provide a joint oncology program. The T-BRCC has its own administrative, nursing, radiotherapy, financial, information systems, health records, clerical, medical physics, and associated support staff. Whenever advisable or when the possibility of ambulatory consultation was possible, support services of the SMC were included on site, e.g. psychology, social work, pharmacy, nutrition, and chaplaincy. The T-BRCC's current physical size is 72,400 gross square feet (GSF).

Our aim is to increase from 2500 to 5000 new patients registered annually which would require significant additional resources. In general, we would need an increase in service areas in the T-BRCC of between 50% to 100%. The new facility planned to accommodate such growth calls for an increase in GSF of 91%, resulting in a total of 130,600 GSF.

The following paragraphs highlight some of the more interesting areas of the expansion.

The increasing patient load will necessitate an enhancement to the outpatient consultation and assessment clinics, and associated waiting areas. With the refinement of individual clinic functions, the incremental number of rooms in the outpatient area will only be five, or an increase of approximately 40%.

The refinement associated with the outpatient department will include establishing of a separate area for professional counselling. The increased use of chemotherapy, either as an adjuvant or as direct treatment, requires larger service and counselling areas for the oncology satellite pharmacy, and an approximately 65% increase in the amount of space for chemotherapy treatment rooms.

In radiotherapy, there will be an increase in the number of treatment machines by six and the number of simulators by two. The number of treatment machines is determined by using a planning criterion of 400 annual new radiotherapy patients per treatment machine. Areas associated with radiotherapy planning, treatment, quality assurance or machine maintenance – medical physics, mould rooms, dosimetry – will increase in proportion to the number of treatment machines. The total capital cost of the additional treatment machines and simulators is approximately $7,700,000.

Surgery continues to be the most common method for treating cancer. With the advent and increased use of intercavity and interstitial radioactive sources, and intraoperative external-beam irradiation, there has been reconsideration of establishing operating rooms in the regional cancer centres. The T-BRCC already has a small room for procedures done under local anesthetic and an adjacent satellite pathology laboratory to facilitate diagnosis and treatment. The number of such procedures is expected to increase. In addition, the equivalent to a shielded operating room would be built in a radiotherapy treatment machine bunker. Either high-energy radioactive sources or a direct high-energy beam from an adjacent radiotherapy machine could be used to treat patients.

The required number of radiation oncologists, medical oncologists and non-staff consultant specialists would increase in proportion to the patient volume. Clinical trials would continue to be a major component of the T-BRCC's research. As well, in keeping with the decision regarding basic clinical research at other regional cancer centres, seven laboratories are planned for the T-BRCC. The T-BRCC will invest part of its expanded energy in increasing its relationship with community cancer clinics in order to promote the highest quality of cancer care.

The expansion of the T-BRCC could be accomplished by summer of 1989 without compromising the current volume of ambulatory oncology patient care in the existing building. The total cost of the expansion, including major equipment, contingencies, furnishings and fees and disbursements, would be approximately $22,700,000.

H.B. Wodinsky, M.H.Sc.
Administrator

WINDSOR

Finally in late 1986 the bunker was built and a linear accelerator installed at the Windsor Regional Cancer Centre. We expect it will be commissioned in late spring of 1987. Although the Windsor Centre was the first clinic in Ontario to have the rotational Cobalt-60 treatment machine in the early 1950s, unfortunately it had fallen behind and was the last centre to have a linear accelerator. Nevertheless, the addition of this new equipment will complete Windsor's basic requirements for radiation treatment.

The Windsor Centre organized a chemotherapy service in 1971. Within a few years, it had become one of the busiest chemotherapy departments among all the cancer centres. The most serious problem was working space. In the late 1970s, a local architect estimated that additional 36,600 square feet of space were needed at that time. It was planned to demolish the then-vacant School of Nursing across from the Windsor Centre's parking lot to construct a new free-standing centre. Funds however were not available then. As a compromise, minor renovations were done on the existing clinic floor and we expanded to the first floor directly above. The first floor then became the new medical oncology service area. To provide space for the medical records office, we took over approximately 600 square feet from the hospital cafeteria and created the Centre's Medical Records Department. It is understood that if the Metropolitan General Hospital needs the space in future we must vacate both of these areas.

With the increase of patient load as projected by the Division of Epidemiology and Statistics, additional personnel will be needed for both medical and office staff. In the next few years, it will be necessary to add at least one radiation oncologist and probably another medical oncologist. We are extremely short staffed in the Medical Records Department. The installation of the linear accelerator makes it necessary to have a second medical physicist, an additional radiation technologist as well as a dosimetrist. Finally, to service the linear accelerator, the Centre will need an electronic technician on staff.

The current trend in cancer treatment is to provide prevention and education as well as psychosocial services. The existing medical staff is barely able to cope with daily clinical work of treaments and consultations, as well as clinical research. It is not reasonable to expect them to take on this extra load; thus new staff members will have to be added in order to provide these additional services.

For some time we have had under discussion proposals for academic affiliation with the University of Western Ontario. We hope that this relationship will be finalized within the coming year.

All of the above underline the urgent need for additional space at the Windsor Regional Cancer Centre. Ideally these needs would be met by the construction of a free-standing centre. The current centre has undergone two expansions during the past 20 years and the architect believes that another expansion on the present site would not be functionally effective or practical.

Another critical concern in Windsor is the lack of a CT scanner for treatment planning. Although another hospital in Windsor has a CT scanner, it is never made available to us for treatment planning because it is always fully booked for other diagnostic procedures. The Essex County Health Council had given approval for a CT scanner at the Metropolitan General Hospital and, almost two years ago, recommended the same to the Ministry of Health. Unfortunatelly, after prolonged discussions, the request was not approved. Without the use of a CT scanner, some of the radiation treatment planning will never be satisfactory.

G.C.K. Mok, M.D.
Director

EDUCATION

SUMMARY OF OCTRF EDUCATION ACTIVITIES

Director of Research and Education

In 1986, the Foundation established a new position -- Director of Research and Education -- and was fortunate enough to enlist the services, on a part-time basis, of Dr. J.C. Laidlaw, former Dean of Medicine at McMaster University. Dr. Laidlaw has also been appointed Executive Director (Medical Affairs) of the Canadian Cancer Society (National Office).

Undergraduate and Postgraduate Professional Education

The Foundation contributes to undergraduate medical education through the Ivan H. Smith Memorial Studentships (see further on).

The Foundation supports postgraduate medical education through funding of a minimum of 15 residency posts in oncology (medical or radiation) at a cost of approximately $500,000 annually. These residency posts are supplementary to those funded by the Ministry of Health at the five medical schools in the Province. In spite of this fiscal support, the chronic manpower shortage continues in oncology, particularly radiation oncology.

Ivan H. Smith Memorial Studentships

In 1986, in co-operation with the Canadian Cancer Society Ontario Division, the Foundation supported 20 studentships for periods of 4 to 12 weeks. This program introduces the future physicians of Ontario to the many rewarding aspects of a career in oncology through observing and participating in the activities at the regional cancer centres. These studentships also can be taken as electives. In 1986, all studentships were taken outside of the academic year except for one elective. Participating centres were: Hamilton, Kingston, London, Ottawa, Toronto-Bayview, Windsor and the Princess Margaret Hospital. In addition, one research-oriented studentship was taken at the Foundation's Head Office (Toronto) in the Division of Epidemiology and Statistics.

The Harold E. Johns Summer Studentships in Medical Physics

In 1986, 13 studentships were taken in the following centres: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, Windsor, and the Princess Margaret Hospital. This program, which is intended to stimulate the entry of medical physicists into oncology, is funded from a special cancer services improvement grant from the Canadian Cancer Society Ontario Division.

Continuing Medical Education

The "phone-in" cancer information service, established jointly by the Foundation and the Canadian Cancer Society Ontario Division has proven to be valuable. Accordingly, the service will be expanded throughout Ontario in 1987.

In 1986, active programs for continuing education were carried out in the regional cancer centres and at the Princess Margaret Hospital through clinic days, seminars, guest lectures and lectures in the community by staff members.

On Ocotber 7, 1986, Dr. Basil Hilaris, Chief of Brachytherapy Service, Memorial Sloan-Kettering Cancer Center, New York, delivered the MacLaren Memorial Lecture at the 24th OCTRF Clinical Conference held in Ottawa. Topic of the lecture was "Interstitial Radiotherapy".

Also at the 24th OCTRF Clinical Conference the Harold G. Vail Lecture was delivered by Dr. Lawrence Weed, Professor Emeritus of Medicine, University of Vermont, titled "Knowledge Couplers in the Diagnosis and Management of Medical Problems".

During the Annual Meeting of the Canadian Oncology Society in September 1986 in Toronto, Dr. D.E. Bergsagel, Chief of Medicine, Princess Margaret Hospital, delivered the W.G. Cosbie Lecture. His subject was "The Treatment of Plasma Cell Myeloma".

The Fifth Eleanor Leder Fund Lectureship in Oncology was delivered on November 25, 1986, at the Toronto General Hospital, by Dr. J.W. Singer, Chief of Oncology, V.A. Medical Center, Seattle, Washington. Dr. Singer Spoke on "Hetergeneity in Acute Leukemia".

The 1986 exchange visitor to Israel, sponsered under the Joseph J. Schiffer Exchange Program, was Dr. Alan Bernstein, Head, Division of Molecular and Developmental Biology, Mount Sinai Hospital Research Institute, Toronto. (This program is sponsored jointly by Mount Sinai Hospital and the Foundation.)

The Foundation sponsored oncology topics at the Annual Scientific and Business Meeting of the College of Family Physicians of Canada, through a "grant-in-aid of special meetings". Dr. Michael Jewett, Chief of Urology, Wellesley Hospital, Toronto, addressed the meeting on "What's New in Cancer of the Prostate?". Dr. John Scott, Director of Palliative Supportive Care, Women's College Hospital, Toronto, delivered an address entitled "Update on Palliative Care".

Two Ontario Cancer Foundation Lectures were awarded in 1986. On June 23, 1986, at the Annual Meeting of the Canadian Congress of Laboratory Medicine in Kingston, Dr. C. Crum of Columbia University, New York, spoke on "The Management of Patients with an Abnormal Pap Test". At the Annual Convention of the Ontario Association of Pathologists held in Alton, Ontario, in October 1986, Dr. D. Pantalogy, Head of Hematology, Toronto Western Hospital, gave a slide seminar on hematopathology.

Mary Lou Erochko

24th OCTRF CLINICAL CONFERENCE

NEW APPROACHES TO CANCER MANAGEMENT

In Ottawa on October 7, 1986, the 24th Clinical Conference of the Ontario Cancer Treatment and Research Foundation provided a state-of-the-art review of cancer management for some 230 registrants. For the morning session the topics and speakers were: (a) Advances in Tumor Diagnosis and Evaluation – Drs. M. Henkelman (OCI) and A. Girard (Ottawa Centre); (b) Future Directions in Therapy of Cancer – Drs. B. Hilaris (Cornell University), and J.F. Kotalik (Thunder Bay Centre); and (c) Hyperthermia – Drs. G.P. Raaphorst and C. Danjoux (Ottawa Centre), and J. Oleson (Duke University). The afternoon session was on Medical Oncology and the speakers were: Drs. D. Stewart (Ottawa Centre), M. Minden (OCI), and J. Mulshine (NCI Bethesda). The Vail Lecture – Knowledge Couplers in the Diagnosis and Management of Medical Problems was delivered by Dr. L. Weed (University of Vermont).

The following summaries include data presented at the conference.

NEW METHODS OF IMAGING*

R.M. HENKELMAN, M.D.**, *Toronto, Ontario*

Over the last 15 years, beginning with the development of computed tomography in the early 1970s, medical diagnostic imaging has undergone a remarkable technological revolution. This period of rapid change continues. It is timely to inquire whether these technological improvements in diagnostic imaging represent a genuine improvement in cancer management.

There are many examples of technological advances. Drs. J.W. Hunt and F.S. Foster have made improvements in the lateral resolution obtainable in ultrasound imaging. They have developed a conical transducer[1] for ultrasound imaging of the breast (Fig. 1), which is being evaluated in clinical trials.

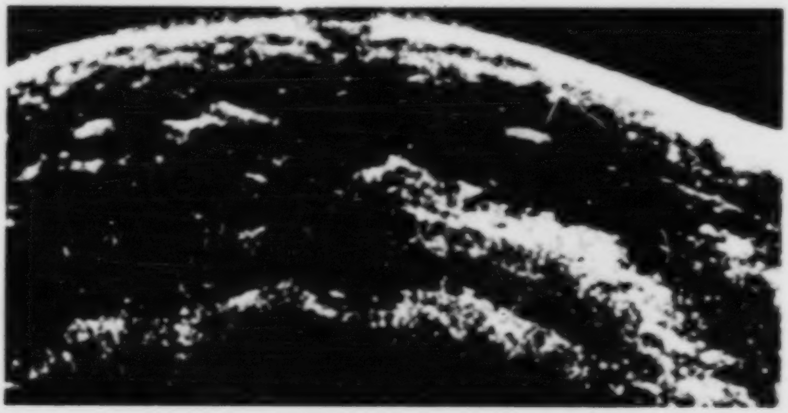

Fig. 1 A high resolution ultrasound breast image showing a ductal carcinoma as a dark void.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Senior Physicist, Princess Margaret Hospital, Toronto; and Professor of Medical Biophysics, University of Toronto.

Drs. P.C. Johns and M.J. Yaffe have developed dual-energy mammographic techniques[3], which identify microcalcifications in breast tumors without the conflicting clutter arising from soft-tissue structures (Fig. 2).

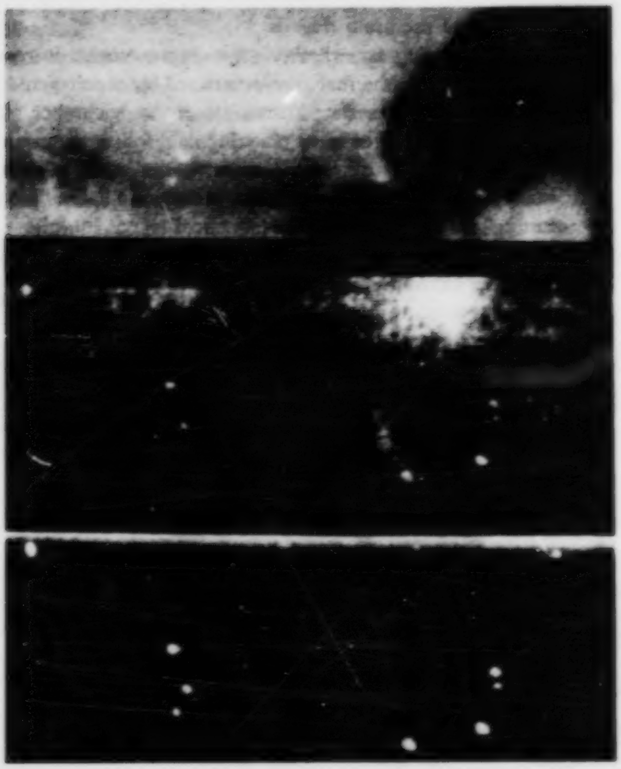

Fig. 2 Single energy breast mammogram (top) in which the clarity of the microcalcifications can be improved with dual energy techniques (centre). Location of microcalcification for reference (bottom).

The greatest change in medical diagnosis in the last five years has been the development of magnetic resonance imaging (MRI). From the stage of an early laboratory prototype in 1980, it has advanced to become an essential part of clinical diagnostic imaging. Ongoing areas of development include improved spatial resolution to submillimeter levels from selected regions of the body such as the orbits, knees, and spinal cord. The use of arbitrarily oriented planes can help to determine the three-dimensional characteristics of tumor volumes.

Obliquely-oriented images give real advantages in cardiac studies and in peripheral limb and disc imaging. Sometimes the unique contrast achieved in MRIs distinctively highlights tumors. On other occasions, the intrinsic contrast arising from flow allows differentiation of major vessels from enlarged nodes. Its ability to avoid interfering artifacts from hard bone makes MRI ideal for imaging for the spinal cord and the base of the brain (Fig. 3).

However, it is important to ask whether these improvements in resolution, contrast, and clarity are meeting the real problems raised by oncological imaging. Diagnostic imaging plays a role in cancer management at a number of levels: screening, diagnosis, staging and treatment planning, and follow-up and monitoring of therapy. To improve cancer management, technical developments in imaging must demonstrate particular characteristics. Improved sensitivity is necessary for screening, but it must be at low financial cost. In spite of good differentiation of tissues in the breast, MRI is too expensive to be used as a screening tool. Specificity is important for diagnosis and staging, but it must be specificity which is superior to that achieved with competitive modes. For example, at the present stage of our development, CT performs just as well as MRI[3] in the identification of metastatic disease to the mediastinum (Fig. 4). In spite of the increased sensitivity of MRI in the diagnosis of liver metastases, it does not outperform CT and even radionuclide scanning in this diagnostic problem.

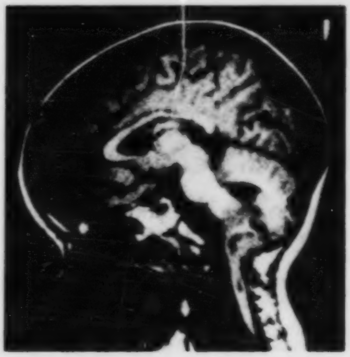

Fig. 3 Magnetic resonance image of a pediatric brain showing excellent visualization of the base of the brain in sagittal presentation.

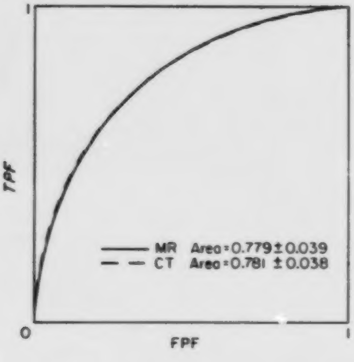

Fig. 4 Comparison of the performance of CT and MR in the identification of mediastinal involvement from primary bronchogenic carcinoma.

Thus, it is becoming increasingly apparent that as long as new developments in imaging are making their contributions to diagnosis or staging on the basis of anatomy and geography, it is unlikely that they will significantly change cancer control. Identification of metastatic disease is done on microscopic grounds and it will not be improved with improvements in spatial resolution from 1 mm to 1/2 or even 1/10 mm.

Thus, I believe that what oncological imaging needs is not better anatomical definition, but other kinds of information: functional information, tissue characterization, physiological information. There are a number of areas where some of the advances in imaging promise to provide this kind of information. As an example, Fig. 5 shows an MRI angiogram in which the contrast of the blood in the vessels arises simply because the blood is moving[4]. It is likely that techniques of this type can be adapted to measure the perfusion of tumors rather than simply their size and shape. Such information would have important consequences for oxygenation for radiotherapy, ability to deliver chemotherapy and heat transfer from hyperthermia.

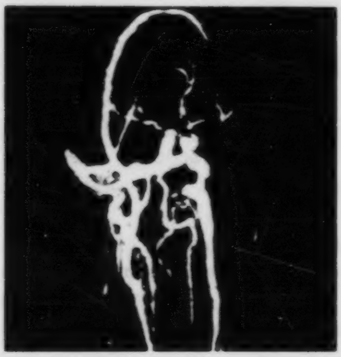

Fig. 5 **Magnetic resonance angiography of the carotid vessels taken without injected contrast.**

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VOLUME ASSESSMENT OF TUMORS*

A. GIRARD, M.D.**, *Ottawa, Ontario*

Tumors are measured to reach a quantitative evaluation of the number of cells and thus help to determine prognosis, which can be related to the number of tumor cells, and to assess and compare treatment results, because the decrease in cell number after treatment correlates with the results.

For that we need a precise and quantitative method of measurement. The ideal method would be to measure the tumor volume (the number of cells equals the tumor volume divided by the volume of one cell).

Until recently, oncologists rarely had access to the full three dimensions of a tumor. If the tumor was superficial, it was possible, by inspection and palpation, to define its width and height, but practically never its depth. If the tumor was deep-seated, the traditional methods of imaging always showed only a two-dimensional projection.

When a consensus was achieved on a standard quantitative method of measurement, the method chosen was two-dimensional. To assess tumor size, the UICC calculates the product of two diameters – one the longest diameter and the second the longest diameter perpendicular to the first.

In practice, frequently one cannot measure even these two dimensions, hence one may measure only one. It is now standard practice, in clinical trials, to combine the uni-dimensional and bi-dimensional methods. A current protocol gives a good example of this practice:

"The criteria for partial remission are:

- 50% or greater decrease in the sum of the products of the diameters of the measured lesions...
- For uni-dimensional lesions by chest x-ray, there should be a reduction of 50% of the measurable dimension."

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**Head, Department of Radiation Oncology, OCTRF Ottawa Regional Cancer Centre, General Division; and Assistant Professor of Radiology, University of Ottawa.

It should be obvious that mixing one- and two-dimensional measurements causes gross inconsistencies, because the area of a circle is related to the square of the diameter, and the volume of a sphere is related to the cube of a diameter (Table I).

TABLE I
Methods of Representing Tumor Size

One-dimensional:	One diameter	$= D$
Two-dimensional:	Area of a circle	$= 1/4 * Pi * D^2$
Three-dimensional:	Volume of a sphere	$= 1/6 * Pi * D^3$

For example, because the volume is correlated directly to the number of cells, if one were trying to assess a partial response, i.e., a 50% decrease in size by the one-dimensional method, we would be describing an 8-fold decrease to 12.5% of the original number of cells. The two-dimensional method would describe a much smaller decrease to only 36% of the original number (Table II).

TABLE II
Partial Response vs Method of Measurement

DIAMETER	AREA	VOLUME
50%	25%	12.5%
71%	50%	36.0%
80%	64%	50.0%

We might think the UICC recommendations (expressing the size of a tumor as the product of two diameters) would give fairly precise results, but this is not so. Indeed, when we assume that tumors of the same cross-sectional area contain the same number of cells, we are making two implicit, and usually incorrect, assumptions.

First we assume that the cross-sectional contour of tumors is usually regular. This frequently is not true. A round tumor could easily contain five times the number of cells present in a highly irregular mass with the same circumference, even though the product of two diameters gave the same value.

Also we assume that tumors are all spherical or, at least, have all the same elongation. This also is incorrect; some tumors are round, but many become elongated to follow the anatomical contours.

Consequently, even when we follow the UICC recommendations, we may introduce large errors in any clinical study that has partial response as one of the endpoints.

Fortunately, new methods of imaging, namely CT scan and for some MRI, make it possible to visualize tumors in their three dimensions and to measure tumors by volume. In theory, this should be a significant improvement. How is it in practice?

To obtain an overview of its clinical relevance, we have done volume assessment in various cancers, using the standard method of integrating the partial volumes of CT slices. This work confirmed our initial impression that measuring the tumor volume was practical, feasible and useful in clinical practice.

In those cases where it was difficult or impossible to calculate tumor volumes, we explored the validity of calculating volumes other than that of the tumor itself. Three types of volume appeared to be useful in oncology: the volume of the tumor itself; the volume of the organ containing the tumor; and the volume of the structures in the vicinity of the tumor.

Tumor Volumes

Measuring tumor volumes is particularly useful in irregular tumors and large tumors – two situations where two-dimensional measurement seems particularly inadequate.

Irregular tumors. Whether clinically or from CT scans, it is difficult to measure irregular tumors precisely, because it is hard to choose the proper diameter for measurement. In addition, one does not take into account the third dimension, which is usually also irregular. Volume assessment is not affected by these problems.

Large tumors. Frequently, these tumors are difficult to measure because in a CT scan they extend over many slices; when they grow, the difference may not be apparent on any individual slice, but mainly on the number of slices affected. Volume assessment, which integrates the partial volume of all the slices, is likely to give a more precise and more reproducible measurement.

Volume of the Organ Containing the Tumor: Liver Metastases

Clinical evaluation of liver metastases is observer-dependent and notoriously unreliable, hence we thought that volume assessment might be useful.

When there are only one or a few well-circumscribed tumors, assessment of total volume is fairly easy and reliable.

Unfortunately, in many cases, metastatic involvement of the liver is so diffuse that one cannot delineate the tumor accurately for volume calculation. In those cases, we attempted to compare the volume of the whole organ, because we know that the total size of the liver increases with its tumor involvement.

In six patients from a Phase II clinical trial of chemotherapy in liver metastases, we measured both the tumor volume and the total liver volume. In those in whom tumor volume could be assessed reliably, there was a good correlation between the tumor volume and the total volume of the liver (Fig. 1).

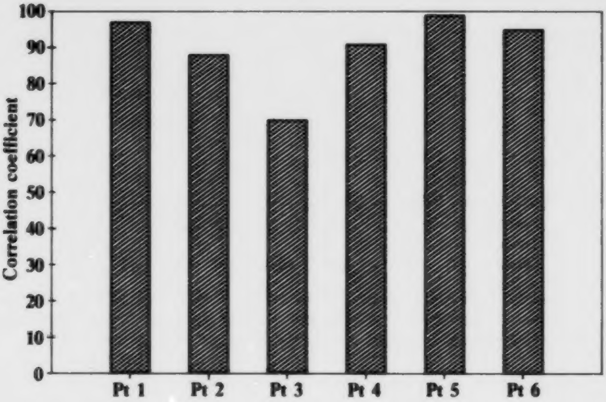

Fig. 1. Correlation coefficient of the evolution of tumor volumes versus that of total liver volumes in six patients with liver metastases from carcinoma of the colon.

An important practical advantage of calculating whole organ volume is that, while contouring the metastases might be difficult, doing the contour of the liver is easy and can be done reliably by a trained technician.

Volume of Structures in the Vicinity of the Tumor: Brain Tumors

More precise measurement is urgently needed in brain tumors. In some cases, the tumor is well delineated and its volume can be measured easily. Frequently, however, and especially when the tumor has been treated, it is difficult to differentiate the tumor from other high-density changes, and edema from other low-density changes. Then treatment decisions must be based on unreliable interpretations of CT scans.

In these cases, one cannot measure the total volume of the organ because total brain volume is fixed by the skull. We tried, instead, to measure, in addition to tumor volume, the volume of different other brain "compartments" in the vicinity of the tumor.

In cerebral gliomas treated by different means, we measured on serial CT scans the following volumes: tumor, edema, total abnormalities, and ventricles. These volumes were plotted versus time.

The first case, Fig. 2, a patient with a low-grade glioma corresponds to what we would expect. After the tumor is excised, its volume goes down to zero and the ventricles, which were compressed, return to normal volume. After a remission, the tumor starts to grow again and is associated with edema. To accommodate this excess substance, the ventricular volume decreases. The tumor continues to grow despite treatment and, finally, the patient dies.

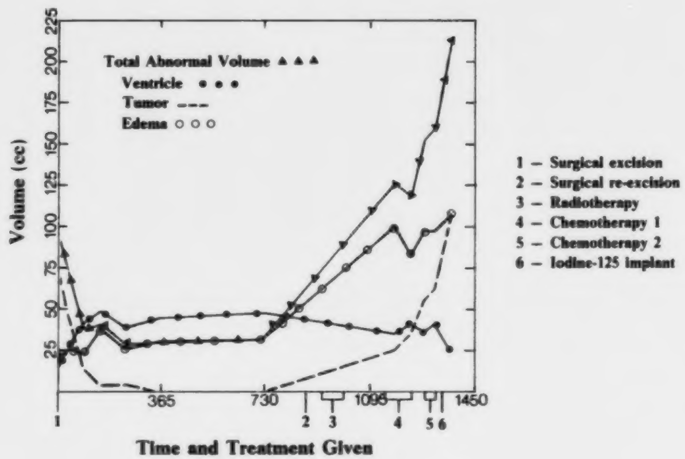

Fig. 2. Low-grade astrocytoma: Volume changes versus time change of different volumes (all visible abnormalities, ventricular cavities, edema, and tumor) versus the time of different treatments.

In the second case, Fig. 3, a patient with a frontal glioblastoma, volume analysis brings some unexpected results. Again, after the tumor is excised, the tumor volume decreases although there is a residual high-density lesion. Subsequently, the ventricular volume returns to normal size. The patient then receives radiotherapy, but shortly afterwards deteriorates and a CT scan is interpreted as showing evidence of progression. Based on this, the patient receives different courses of chemotherapy and dies on day 300.

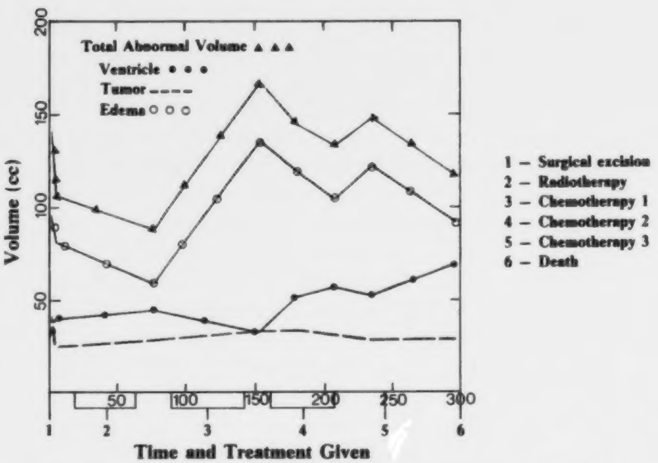

Fig. 3. Glioblastoma multiforme: Volume changes versus time change of different volumes (all visible abnormalities, ventricular cavities, edema, and tumor) versus the time of different treatments.

When we analyze the evolution of the volumes of the different compartments, we find a puzzling pattern. Initially, in association with the increase in low-density changes, there is a corresponding decrease in ventricular volume, compatible with space occupying edema. Subsequently, however, although a large volume of low-density changes remains, the ventricular volume begins to increase and continues to increase until death. In a cavity of fixed volume like the skull, and in the absence of other signs of hydrocephalus, an increase in ventricular volume means a decrease in extraventricular cranial content. Although there is no autopsy confirmation, it is tempting to speculate that the clinical evolution and the low-density changes detected on the CT scan might represent not tumor evolution but white matter changes and subsequent atrophy related to treatment.

In clinical practice, it is essential to analyze the evolution of sets of clinical parameters "syndromes" to understand conditions where no individual parameter is by itself diagnostic. In the same way, these two examples illustrate that, in brain tumors, evaluation of a set of volumes plotted against time on a single graph might bring to light diagnoses that otherwise would be missed. A similar approach in other types of tumor might permit us to detect similar useful volumetric patterns.

In conclusion, although CT-derived volume assessment is still time-consuming and costly, its use already is justified in those cases where a precise evaluation of the size of the tumor is important, for example, in clinical trials. It is certain, moreover, that with advances in imaging techniques, it will become easier and cheaper. I am convinced that, in a few years, because of the important flaws related to one- or two-dimensional measurements, volumetric assessment will be recognized as the only acceptable method of evaluating tumor size in oncology.

BRACHYTHERAPY: INTERSTITIAL RADIOTHERAPY*

BERT MacLAREN MEMORIAL LECTURE 1986

B.S. HILARIS, M.D.**. *New York, N.Y.*

Radium was discovered by the Curies in 1898 and promptly was applied in therapy. Thus the entire history of interstitial brachytherapy encompasses only some 80 years.

Early physicians had little understanding of the biological effects of radium. In the early 1920s Quimby recognized that any definite number of milligrams of radium always emits the same amount of energy per hour. Thus for some time dosage was specified in terms of milligram-hours. Within a few years, dosage tables, notably those of Paterson and Parker in Manchester and Quimby at the Memorial Sloan-Kettering Cancer Center (MSKCC) Hospital, gave the doses in terms of roentgens. In 1931 Forsell proposed the term "brachytherapy" but other terms have been used to describe treatment by radionuclides viz plesiotherapy, curietherapy, endocurietherapy, etc. The handling of the radioactive sources involved substantial hazards of radiation exposure and a number of ingenious techniques, such as afterloading of the radioactive sources, have been devised to decrease radiation exposure. Afterloading techniques have increased the use of interstitial and intracavitary radiation, while reducing the hazard of occupational radiation exposure.

The present era of brachytherapy is characterized by many technical refinements and innovations, such as: afterloading of radioactive sources; use of nuclear-reactor-produced radionuclides as substitutes for radium and radon; advances in brachytherapy dosimetry; extensive use of computer technology; and adaptation of newer imaging methods.

Most contemporary brachytherapy is carried out with radionuclides such as cesium^{137}, iridium^{192}, iodine^{125}, and gold^{198}. These artificial radionuclides have low photon energy as compared with radium, and hence result in reduced radiation exposure. Compared with 1604 years for radium^{226}, they have a relatively shorter half-life, ranging from 2.7 days for gold^{198} to 30 years for cesium^{137}. One may achieve intense, highly localized deposition of ionizing radiation by the interstitial or intracavitary needles, wires, capsules, or ribbons containing articidial radionuclides.

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**Chief of Brachytherapy Service, Memorial Sloan-Kettering Cancer Center, New York, N.Y.; and Professor of Radiology, Cornell University, Ithaca, N.Y.

The physical distribution of such sources is critical to the desired dose distribution throughout the target volume. The introduction of the computer technology in brachytherapy dosimetry and the resulting ability to generate radiation dose distributions at numerous points and planes within the target volume has increased tremendously the accuracy of brachytherapy. Recent advances in diagnostic imaging techniques, especially computerized tomography, permit one to define normal and neoplastic tissues in three dimensions. These advances have greatly improved the planning of brachytherapy and have improved our ability to display large amounts of information, whether related to diagnosis or the calculated radiation dose distribution. The role of brachytherapy is thus undergoing a re-evaluation and expansion.

The generally lower brachytherapy dose rate, as compared with external radiation, allows more efficient repair and repopulation in the normal tissues. The higher absorbed dose delivered over a short period, results in a lower surviving cell fraction than with equal doses delivered by external beam.

Brachytherapy procedures are performed under local or general anesthesia in the operating room, and usually the patients are hospitalized for a variable period. The tumors treated by this technique usually are localized, less than 4 to 5 cm in size and have slow doubling times. The three-dimensional distribution of the radioactive sources in the target volume is highly critical because the radiation dose diminishes rapidly within a very short distance from each source. Small departures from proper spacing may result in "overdosage" with ensuing tissue necrosis, or "underdosage" and inadequate tumor treatment. Precise localization of radioactive sources is done by orthogonal radiographs in two planes or by stereoshift methods. The location and orientation of the sources is entered into the computer in relation to target-volume coordinates and then one can make rapid, precise calculations of dose distribution.

Contemporary Results of Brachytherapy

Brachytherapy can cite extensive and convincing evidence of its ability to cure malignant tumors in several sites.

Most head and neck cancers, because they are accessible, are suitable for management by brachytherapy alone (T1) or in combination with external radiation (T2, T3). For early lesions, the overall 5-year survival rates are in the range of 80% to 90%. The survival rates generally vary with the anatomic sites and the extent of the disease (65% to 95%). Good results have been obtained in early cancer of the anterior two-thirds of the tongue and floor of the mouth.

In early prostate cancer, brachytherapy alone can control local disease in 8 of 10 patients and achieve 10-year survival rates similar to external beam or surgery, with decreased urinary or bowel morbidity and sexual dysfunction.

In early cancer of the bladder (T1), van der Werf Messing has achieved an 80% actuarial 10-year disease-free survival after brachytherapy (195 patients) in contrast to about 35% after TUR only (144 patients). In the TUR group, 72% had at least one bladder recurrence; in the brachytherapy group, only 18%. Unfortunately, this technique is not widely used in North America.

In early cancer of the breast, interstitial brachytheapy is used to boost the radiation dose to the primary site following lumpectomy and moderate doses of external-beam radiation. In France between 1961 and 1977, Pierquin treated 408 patients with T1, T2 and T3 breast tumors with excellent local control. At 10 years, the local and regional recurrence rate was 8% for patients with T1 lesions, 9% for T2 lesions and 15% for T3 lesions. In the United States, Helman, using a similar approach, obtained a 6-year rate of local tumor control of 96% for Stage I and 90% for Stage II. Both groups reported the esthetic results were good to excellent.

In soft-tissue sarcomas, an alternative to amputation is brachytherapy – in the form of iridium temporary implants, combined with conservative surgery. At MSKCC Hospital, early results show that local control and survival with this approach are comparable to those obtained by the combination of conservative surgery and external-beam radiation. A randomized study is being done at MSKCC to evaluate further the usefulness of this technique.

Our experience shows that brachytherapy can control 60% to 80% of localized non-small cell lung cancer, depending on the tumor volume. Patients with T1, T2 unresectable tumors treated with brachytherapy have a 33% 5-year survival.

At MSKCC we have demonstrated that interstitial brachytherapy of localized cancer of the pancreas results in about 30% survival at 2 years.

Directions of Future Promise

Combined treatment is being explored in a number of clinical situations.

Brachytherapy is used with conservative surgery to achieve organ preservations – in cancer of the breast, soft-tissue sarcomas of the extremities, bladder and prostate. Early reports indicate that this combinations improves long-term results.

Intensive studies are under way to compare low-dose-rate brachytherapy alone to low-dose-rate brachytherapy and hyperthermia, but a great deal of work remains to be done.

Brachytherapy is being used in combination with chemotherapy in an increasing spectrum of tumors. The spontaneous development of drug-resistant mutations increases with time and may be as crucial in cancer chemotherapy as in that of microbial infections. Therefore, it is probable that initiation of chemotherapy simultaneously or even before the attack on the primary tumor will give a much better chance for cure. As new chemotherapeutic agents become available with efficacy against a variety of neoplasms, it seems probable that such combinations will be used in tumors of bladder, pancreas, lung, esophagus, etc. Tumor models developed in the laboratory appear to offer a reliable quantitative approach for the evaluation of various combinations of brachytherapy, chemotherapy and/or immunotherapy; these aim to eradicate tumor cells at local and distant sites, while decreasing the morbidity associated with treatment for cure by one modality alone.

In the future, intensive efforts will be needed to develop or adapt existing technology to the applications of brachytherapy; to allow more precise tumor and critical normal tissue delineation; and to develop and investigate new radionuclides suitable for brachytherapy.

The achievement of these goals will have a great impact on the future use of brachytherapy alone or in combination with other modes of cancer treatment.

References are available upon request from:

Dr. Basil S. Hilaris
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, N.Y. 10021
USA

ALTERED FRACTIONATION SCHEMES IN RADIOTHERAPY*

J.F. KOTALIK, M.D.**, *Thunder Bay, Ontario*

When radiotherapy was first introduced about 100 years ago, therapists employed both large single doses and treatments divided into several fractions. Later, it was proved experimentally that tumor control could be improved and undesirable side effects on normal tissue reduced if treatment was fractionated. For some time, some workers gave treatments for several times a day for up to seven days a week. On the basis of accumulated clinical experience and perhaps also for convenience, we came to accept schedules consisting of one session per day, dose of 180 to 250 cGy per fraction, every working day of the week and for several weeks in a row. This is routine, conventional fractionation, when cure is the intent.

However, over the last 30 years, radiobiological investigations have demonstrated that any size of fraction, any interval in between and any number of fractions or even continuous irradiation may be the most advantageous, depending on the tumor and its host.

For most common clinical situations, radiobiological factors favor increased fractionation above that which is conventional – generally decreased dose per fraction and treatment two or three times per day. Such regimens should prevent regeneration of tumor during radiotherapy and should take advantage of the fact that fast-cycling tumor cells would be more deeply sensitized by each fraction than would the slowly cycling cells responsible for late side effects of radiation. The oxygen enhancement ratio appears to decrease as dose per fraction decreases so that this should reduce the resistance of hypoxic tumor cells and improve their reoxygenation. Also, with an increased number of fractions, the admixture of hypoxic tumor cells becomes less important. Finally, after radiation the oxygenated cells of normal tissue seem to recover from sublethal damage faster and more effectively than the hypoxic tumor cells. If radiotherapy is given three or four hours apart, normal tissue cells will already have recovered and the more resistant but hypoxic tumor cells will not have recovered and will be more susceptible to further damage[1].

However, it is important to note that when we change the fractionation regimen, we change the relationship between early and late effects, as they are commonly encountered. If we use fewer and larger fractions, there would be little change in acute effects and in tumor control but probably a great increase in incidence of late radiation effects. If we use more and smaller fractions, total dose can be increased considerably without increasing late effects as encountered in conventional fractionation. Acute effects will be increased somewhat but so will the degree of tumor control.

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**Director, OCTRF Thunder Bay Regional Cancer Centre.

Clinical observations support these radiobiological conclusions. Almost all studies with larger and fewer fractions show no improvement in tumor control and often show an increased rate of late complications. There may be exceptions, for example in the malignant melanoma, but even this is controversial. Reduced fractionation, however, has its place in situations that call for radiation below the tolerance level of normal tissue because this provides the same degree of palliation with increased convenience and economy. If properly employed, reduced or accelerated fractionation for palliative radiotherapy would benefit the patients and make available more treatment time for patients who require increased fractionation for cure.

There is already considerable clinical experience with increased fractionation, particularly multiple fractions per day, and results have been reported on several thousand patients[2]. Almost all of these reports indicate that tumor control is as good as or better than with comparable conventional fractionation with the same or fewer long-term side effects. Unfortunately only a few of these studies were prospective and controlled; even in those that were, it is impossible to say whether altered fractionation was given in sufficiently high doses to use similar fraction of normal tissue tolerance as conventional fractionation[3,4]. The bulk of published reports describes uncontrolled studies with an endless course of radiotherapy variety of fraction sizes, intervals between fractions, number of fractions and total dose. These demonstrate only that fractionation is feasible and safe but do not offer convincing proof of its superiority.

The most promising series of clinical experiments is being carried out by a Radiation Therapy Oncology Group in the USA. Those trials are testing twice-daily irradiation in carcinoma of the lung, head and neck, and malignant astrocytoma; the dose is gradually escalated until an increasing frequency of side effects demonstrate that the tolerance level was reached. Only when we establish new upper limits of total dose for this altered fractionation will we be able to compare it with conventional fractionation, in an usual Phase III trial.

It is important to distinguish between acute and late reactions in radiotherapy. Late reactions should be the limiting factor when cure is within reach. Here probability of cure should be balanced against probability of permanent dysfunction or disability. To do this, we need early, predictive, quantitative, non-invasive in vivo tests for late damage and accurate clinical scales with which to measure the low incidence (5% to 10%) of these events. Studies should include patients who probably will have long-term survival.

Acute reactions should be judged on a different basis. We have reason to believe that increased fractionation will increase tumor control when the total doses are based on the current incidence of late effects; however acute late effects will also increase. We need to circumvent acute effects so that they may not be dose limiting. We hope this can be done through intensive support of patients on curative radiotherapy, including hyperalimentation, bypass surgery, antibiotics, intensive nursing, etc., just as patients are supported, for example, during bone marrow transplantation.

Systematic investigation of fractionation is required; that means, to select a dose per fraction and interval in between which promises to be effective for a particular tumor site and then escalate the total dose to maximum tolerance for acute effects. Once the late effects are assessed in this group of patients (and they are likely to be mild), the total dose would be escalated to the tolerance for late effects. Intensive support would be supplied through the phase of acute side effects. Only then can we obtain the full benefit of altered fractionation in terms of improved tumor control. This systematic investigation would involve a large number of patients with common tumor sites and similar tumor load; to carry it out in our lifetime would call for a cooperative multi-institutional effort for a decade or so. However, unless we carry out such a systematic investigation of altered fractionation regimens, we will never realize the full potential of megavoltage radiotherapy in local and regional tumor control.

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HYPERTHERMIA: RATIONALE AND TRENDS*

G.P. RAAPHORST, Ph.D.**, *Ottawa, Ontario*

Many studies, using cultured mammalian cells in vitro, have shown that hyperthermia can kill mammalian cells and cause radiation or chemotherapeutic sensitization. The effect of hyperthermia depends on the heating time and temperature. A difference of 1°C can cause a significant change in the degree of cell killing. Experiments in cell biology indicate that hyperthermia as a radiosensitizer may provide a therapeutic advantage when combined with radiation. Such experiments show that hyperthermia is complementary to radiation and kills radioresistant cells, which are hypoxic, at low pH or in the S phase of the cell cycle. Thermoradiosensitization can be divided into two categories: sensitization of radiation-sensitive targets, and the inhibition of repair of radiation damage. Hyperthermia can inhibit the repair of both sublethal radiation damage and potentially lethal radiation damage. This effect is most pronounced when heat treatment is given during or after irradiation, although repair also can be inhibited if sufficiently large treatments are given before irradiation.

Several workers have demonstrated that the cells of radiation-resistant tumors such as melanomas, gliomas, and some sarcomas may have an enhanced ability to repair radiation damage. Therefore, it would be advantageous to use hyperthermia to inhibit this repair when treating radiation-resistant tumors. Experiments with a melanoma cell line in culture have shown that these cells have a greater ability to repair sublethal damage and that hyperthermia can inhibit this process. This consideration becomes more important in the clinic where one gives split doses of radiation for fractionated treatment and where low-dose-rate irradiation is given during interstitial therapy. These methods of radiotherapy rely strongly on the repair of sublethal radiation damage which occurs during split-dose or low-dose rate treatment. Under these conditions, hyperthermia may modify significantly the cell's ability to repair sublethal damage.

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**Chief Physicist, OCTRF Ottawa Regional Cancer Centre; and Assistant Professor of Physics, University of Ottawa.

A considerable body of literature indicates that hyperthermia has an enhanced effect on radiosensitization during low-dose rate irradiation. This effect was most pronounced when the treatments – hyperthermia and radiation – were given simultaneously. Using these premises such combination treatment may have its optimum uses during interstitial radiotherapy.

The Ottawa Regional Cancer Centre is developing a probe which can administer interstitial radiation and interstitial hyperthermia simultaneously. This probe is designed to fit into the small afterloading radiotherapy catheters and will capitalize on the optimum conditions for the maximum thermal enhancement of radiosensitization. In addition, such interstitial application will give better control of the distribution of radiation and heat fields to the tumor.

HYPERTHERMIA: THE OTTAWA EXPERIENCE*

C.J.E. DANJOUX, M.D.**, *Ottawa, Ontario*

The hyperthermia program in Ottawa is a multi-institution endeavor with collaboration from the National Research Council (NRC), Atomic Energy of Canada Ltd., the two universities in Ottawa, and the OCTRF Ottawa Regional Cancer Centre. Two years ago we held a national conference on the physical engineering and clinical aspects of hyperthermia in Ottawa. Since then we have developed a computerized thermometry system, carried out animal experiments and started a clinical trial.

Computerized Thermometry System

Computerized thermometry consists of an IBM PC, a Keathly Data Acquisition System, and a temperature reference operated under a program called ASSYST. All relevant information is recorded and stored automatically for later analysis. During treatment the temperature can be displayed as a profile or as a function of time.

The thermometry probe consists of up to 12 type K thermocouples, arranged in a probe 0.8 mm in diameter. The spacing between thermocouples can be varied. The probe fits in a 16-gauge catheter.

Extensive studies were carried out to investigate the performance of the thermocouples in microwave fields and in differenct catheters.

Animal Experiments

The TAG MED hyperthermia unit (2450 MHz) and computerized thermometry system was evaluated in pig experiments at NRC. The latest experiment in pigs studied the effect of blood perfusion on the temperature profile.

Clinical Study

From December 1985 to June 1986, we carried out a Phase I study of local hyperthermia and radiotherapy in recurrent superficial malignancies using the TAG MED unit and our computerized thermometry system. Since the recurrences were in previously irradiated areas, these patients were given 2000 cGy in 10 treatments over two weeks.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Head, Department of Radiation Oncology, OCTRF Ottawa Regional Cancer Centre; and Assistant Professor of Radiation Oncology, University of Ottawa.

We have treated eight patients. Hyperthermia was delivered twice weekly with a 72-hour interval between sessions to avoid thermal tolerance. Temperature was measured by inserting measuring probes in several locations within the tumor and adjoining normal tissue. To ensure reproducible positioning and avoid repeated invasion of the tissues, the probes were inserted in catheters which remain in place for the duration of the treatment. The maximum lesion size we can treat is up to 5 cm and 2 cm depth. From the 32 hyperthermia treatments to date, we have observed the following:

- The therapeutic temperature is reached in 15 min;
- Temperature in the tumor tended to be higher than in surrounding tissue;
- Temperature gradients of 4° to 8°C have been observed over short distances of 1 cm between thermocouples.

We have observed the following adaptive mechanisms. During treatment we had to increase the power over time to maintain the same temperature. With time there is a gradual separation between temperature points within the tumor and normal tissue. After about 30 minutes, some adaptation usually causes further temperature variation between thermocouples.

Our limited clinical experience suggests that transient erythema and local discomfort can be controlled by reducing the temperature by less than 1°C. We have had no thermal burn or necrosis. In the future we plan to study the effect of perfusion and adaptation in animal experiments.

With a program that now spans the whole spectrum from bench to bedside, we plan to expand our team effort in the laboratory, in pigs, and in the clinic.

HYPERTHERMIA: CLINICAL RESULTS AND FUTURE PROSPECTS*

J.R. OLESON, M.D., Ph.D.**, *Durham, North Carolina*

A number of biological rationales have stimulated investigation into the use of hyperthermia (HT) as an adjunct to radiotherapy (RT) and chemotherapy (CT) in treatment of human malignancy. Clinical data have confirmed that, in bulky tumors, temperature elevation to 42°C enhances the response to RT. Using a variety of treatment schedules, investigators have reported a complete response rate of about 35% in nodules treated with RT alone compared to about 75% with RT plus HT.

Patients selected for HT generally have localized bulky disease unlikely to be controlled with RT alone. HT may be combined with RT for improved palliation, improved local control rates, improved cure rates, or improved operability.

A variety of technical approaches for producing HT can be grouped into whole body, regional, localized, superficial, or localized interstitial techniques, referring to the volume of tissue being heated.

Using the interstitial HT plus RT approach, complete response rates depend upon the minimum measured temperature achieved in the tumor, the radiation dose given, and the tumor volume. These same prognostic factors also correlate with probability of complete response when HT is produced by other techniques.

Available HT techniques do not reliably produce uniformly high temperatures in tumors of various sizes in various sites: current results emphasize the need for improved HT equipment and improved means of determining intratumoral temperature distributions. The best equipment must be determined on a site-by-site basis through clinical trials. However, numerical models, which use computer programs, are being developed to predict performance of various types of equipment and this may facilitate development and clinical application of equipment in the future.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Associate Professor of Radiation Oncology, Duke University, Durham, North Carolina, USA.

The optimal schedules of RT and HT remain to be identified. Indeed, the results of combined therapy do not appear to depend sensitively upon the number of HT fractions given. Conventionally fractionated RT is important, however, because usually there is no enhancement of RT in all volumes containing bulky tumor because of nonuniform temperature distributions.

In large, deep-seated tumors, volumetric regression after RT and HT may be quite slow, suggesting that, for clinical evaluation of HT plus RT, we need alternatives to complete response as endpoints.

In the clinic, we do not have test of the potential therapeutic advantage of combining HT with CT. Phase I and II trials are being started at several institutions to study CT combined with whole body HT or localized HT.

In the future, HT must be tested in Phase III trials which are site-specific and are designed to determine the contribution of HT to local control and survival. HT holds promise for improving treatment results in glioblastoma, advanced head and neck carcinoma, bronchogenic carcinoma, advanced gynecological carcinomas, sarcomas, and melanomas.

NEW METHODS OF DRUG DELIVERY*

D.J. STEWART, M.D.**, *Ottawa, Ontario*

Chemotherapeutic agents frequently exhibit a steep dose-response curve against malignancies; hence, ways have been sought to increase the dose of drug that can be delivered with safety. For localized tumors, local administration should enhance local efficacy by increasing local drug concentrations without increasing systemic toxicity.

Local administration usually will produce an increase in the local peak concentration and in the area under the concentration-time curve (AUC) during its infusion. If the drug is rapidly cleared from the body, it will have a small AUC after intravenous (IV) administration and the increase in AUC achieved by local administration will be quite large when expressed as a per cent of the usual IV AUC. On the other hand, if a drug has a slow total body clearance, the usual AUC will be large and the per cent increase in AUC, following local administration, will be relatively small. Hence, local administration will be more advantageous if the drug has a high total body clearance than if it has a low clearance, if efficacy is more highly dependent on AUC than on peak concentration. Generally one assumes that this is true, although it may not be true in all instances. For example, if drug action requires a threshold effect, peak concentration may be more important.

Another important factor is local blood flow rate. If blood flow to a particular site is rapid, the drug will be diluted and washed out more rapidly than if flow is slow and hence the benefits of local administration will be decreased.

If a drug is eliminated or metabolized by the tissue into which it is infused, systemic toxicity will be less than if drug uptake or metabolism is small. It is probable, however, that when most drugs are infused into most arteries, the local tissues will take up only a small percentage of the drug. An important exception are drugs infused into the hepatic artery; some drugs will be metabolized by the liver.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Medical Oncologist, OCTRF Ottawa Regional Cancer Centre; and Associate Professor of Medicine and of Pharmacology, University of Ottawa.

Combining these factors, $R_d = 1 + \frac{CL_{tb}}{Q(1\text{-}E)}$

where R_d is the relative advantage of local administration of the drug. CL_{tb} is the total body clearance of the drug. Q is the regional exchange rate (example: local blood-flow rate), and E is the fraction extracted during the first pass through that particular tissue. Using this equation, one can predict the probable advantage of a particular drug given by a particular route assuming that, for antitumor activity, AUC is more important than peak plasma concentration.

In addition, if a locally administered drug is to have an advantage, it cannot be given into the organ that is the site of dose-limiting toxicity and the drug must not require hepatic metabolism for its activation.

Routes of drug administration include intravenous, oral, intra-arterial (IA), intravesical, intrathecal, intrapleural, intraperitoneal, pericardial, and intratumoral.

Recently renewed interest has been shown in IA administration of chemotherapy. One would expect that IA administration would be advantageous for many drugs. One would anticipate that there would be a greater advantage to giving a drug into the internal carotid artery, with a flow-rate of 300 ml/min, than into the hepatic artery, with a flow-rate of 1000 ml/min. For any given artery, the advantage would be greater for drugs with rapid clearances such as thymidine, 5-fluorouracil, and BCNU than for drugs such as methotrexate that have a lower clearance rate.

Studies of pharmacology of IA cisplatin have shown increases in both local peak concentration and AUC. Systemic exposure was the same after IA as after IV administration, hence, local exposure is increased without sacrificing potential systemic efficacy. In addition, we have found in human autopsy tissues that tumors which received IA cisplatin have higher platinum concentrations than do tumors that received IV cisplatin. Others have found increased tissue concentrations of agents such as BCNU following IA administration.

Because of the apparent pharmacological advantages of IA cisplatin, we have done a number of studies employing intracarotid cisplatin in patients with recurrent brain tumors. Local retinal and neurological toxicity were dose-limiting, but there was suggestion of improved efficacy. We studied intracarotid cicplatin alone and this agent combined with intracarotid VM-26 and BCNU with and without the concurrent administration of multiple IV antineoplastic drugs. Concurrent intracarotid VM-26 and BCNU appeared to increase efficacy, while the concurrent administration of systemic agents added little. Current studies focus on a more intensive intracarotid schedule combined with different systemic agents.

Also we have done a study of intracarotid mitomycin-C. Local ocular and neurological toxicity was dose-limiting at doses above 15 mg/m^2 . We saw no responses in 6 patients with glioblastomas. However, 6 of 13 patients with recurrent brain metastases have responded; 1 of these has been in complete remission for more than three years. Based on these encouraging results, we are starting a study which will combine intracarotid mitomycin-C with intracarotid VM-26 and cisplatin.

We have also done a study of intracarotid PCNU. Ocular, neurological, and hematological toxicity were dose-limiting at a dose of $110/m^2$. The response rate was only 41% which is no better than that seen with intravenous PCNU. Therefore, we do not plan further studies with intracarotid PCNU.

Our overall impression is that intracarotid drug administration is somewhat more effective than IV administration for intracerebral tumors, although technically it is more difficult and more toxic. However, such an approach should still be considered investigational and should not be used routinely.

In addition to our intracarotid studies, we have also undertaken studies of IA cisplatin for locally extensive bladder carcinoma. In 21 evaluable patients, this approach has given a complete remission rate of 14% and a partial remission rate of 57% for an overall response rate of 71%. The major toxicity has been peripheral neuropathy. IA cisplatin appears to be more active than IV cisplatin against localized bladder tumors, although, again, this has not been proved unequivocally.

In past studies of IA chemotherapy for hepatic metastases, response rates have consistently been higher with IA than with IV administration. It is controversial whether survival is prolonged, but most investigators agree that IA administration increases palliation of hepatic metastases.

Concerning the intrathecal (IT) route, we have shown that an IT combination of methotrexate, cytosine arabinoside and hydrocortisone is well tolerated and, in patients with meningeal involvement by leukemia, appears to be more effective than one or two of these agents. Based on these results, we started a study combining these drugs with IT thio-TEPA in meningeal carcinoma, lymphoma and leukemia. The incidence of possible leukoencephalopathy was higher in this study than in our other studies of IT therapy. In addition, only 50% of patients had neurological improvement. We believe that current therapy is reasonably good for meningeal involvement by leukemia and lymphoma, but we greatly need new treatment for meningeal carcinomatosis.

Intravesical chemotherapy is used frequently for superficial bladder cancers. This will only be effective for very small residual tumors because of the limited penetration of drugs from the epithelial surface. Many different drugs have been tried intravesically in the past, but those most frequently used now are BCG, thio-TEPA, Adriamycin, and mitomycin-C. Recently we started a study of intravesical mitoxantrone because this drug shows a very steep dose-response curve against bladder cancer cells in vitro. We have treated 16 patients who relapsed after intravesical treatment with other agents and saw no toxic effects at doses of 5 or 6 mg. Severe bladder inflammation has been seen at higher doses.

Chemotherapy can be given by a variety of different routes. Work done to date suggests that regional therapy frequently can palliate symptoms from localized malignancies. One would expect increased cure rates only for those tumors which cause death by local extension and in which complete remission can be induced by local therapy. Probably we can prolong survival with local therapy in some situations, but this has not yet been proved unequivocally. Regional chemotherapy is "half-way technology". While it is useful in the treatment of some patients, and while further studies are warranted, it probably will not be needed once we perfect highly active systemic chemotherapy for the treatment of malignancies.

References are available upon request from:

Dr. D.J. Stewart
Ottawa Regional Cancer Centre
General Hospital Division
501 Smyth Rd.
Ottawa, Ontario
K1G 8L6

ONCOGENES, GROWTH FACTORS AND ANTIONCOGENES*

M.D. MINDEN, M.D., Ph.D.**, *Toronto, Ontario*

In the past 20 years, tremendous advances have been made in our understanding of the growth of normal and malignant cells. The study of RNA tumor viruses and the DNA of malignant cells have identified a number of genes capable of transforming "normal" cells to a malignant phenotype. The techniques of molecular biology enabled us to clone these "oncogenes" and made possible studies of the origin and the structure and function of these genes.

DNA similar to the oncogenes was found in normal cells and was found to be expressed in normal cells. In some cases comparison of the gene present in the normal cells with that in the malignant cell has demonstrated alterations in the gene in the transformed cell. The types of changes found may be: point mutation; chromosome translocation; and amplification. Respectively, such changes produce an altered function of the protein, changes in its regulation, and increased amounts of the protein in the cell.

We have determined the localization and function of some of these proteins. For example the protein products of the myc, myb and ski genes are located in the nucleus, the products of the ras genes are found in the cytoplasm, the products of src, erb-B, fms and yes are either associated or integrated into the cell membrane, and the product of the sis gene is secreted.

The function of the product of the sis gene has been well characterized. The sis gene encodes for the beta-chain of platelet-derived growth factor (PDGF), which is required for the growth of a number of cell types in culture. In addition to PDGF, a host of other growth factors with tissue specificity have been identified; these include: nerve growth factor (neural tissue), epidermal growth factor (epidermal derived tissues), IL2 (lymphocytes and hematopoietic tissues), IL3 (lymphocytes and hematopoietic tissues), and tumor growth factor alpha and beta (epidermal derived tissues).

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**Medical Oncologist, Ontario Cancer Institute, Toronto.

Growth factors may interact with their target cells by exocrine (produced by a distant cell and carried by the circulation to the target cell, e.g. erythropoietin), paracrine (produced by neighbouring cells, e.g., TGF alpha), or autocrine (produced by responding cell, e.g., T lymphocytes) routes. Each of these mechanisms functions in normal cells. The autocrine mechanism of growth control has been observed in transformed cells and it may contribute to the development of the malignant phenotype of these cells.

In contrast to the oncogenes which induce a malignant phenotype in an appropriate host cell are "antioncogenes"; those that control the development or expression of the malignant phenotype. Evidence that antioncogenes exist comes from cell hybrid experiments and from observations of genetic forms of cancer. The former suggest that, when introduced into malignant cells, genes on certain chromosomes can suppress the malignant phenotype. Observations in the latter have led us to postulate a set of genes which control the susceptibility to develop a specific type of tumor, such as retinoblastoma or Wilm's tumor. In both cases the loss of these genes leads to the development of malignancy.

Our understanding of what controls the growth of normal and malignant cells has progressed a long way. We have identified genes which control the growth of cells and the predisposition to malignancy. In the future it should be possible to identify people at risk of developing tumors. As well, as our understanding of the biochemistry of the cell improves, we should be able to develop drugs that take advantage of the alterations which occur in the malignant cell.

CLINICAL USES OF MONOCLONAL ANTIBODIES OF LUNG CANCER*

J.L. MULSHINE, M.D.**, *Bethesda, Maryland*

This review will discuss briefly therapeutic applications in lung cancer with emphasis on strategies that will allow more successful outcome. Initially, investigators envisioned that to use monoclonal antibodies, the immunoglobulin would have to destroy the tumor through a direct effect or by mobilizing the immune system. This effect could be augmented by coupling a monoclonal antibody to some other cytotoxic agent such as a chemotherapeutic agent, an immunotoxin or certain radionuclides. For any of these applications, one must consider certain pharmacokinetic issues. In addition, each particular type of application involves specific issues in selection and generation of monoclonal antibodies. The initial 10 years of experience with monoclonal antibodies has not generated a monoclonal that binds exclusively to tumor tissue. In general, investigators have come to accept that monoclonal antibodies will recognize certain amounts of normal tissues in addition to the target tumor cells. Therefore, those who design clinical trials with monoclonal antibodies face a problem similar to that encountered in studying chemotherapeutic agents. Both of these modalities, because they affect normal tissue, would be expected to have certain toxic side effects, and the design of clinical trials would attempt to maximize tumor-cell kill while sparing normal structures. In keeping with this limitation of monoclonal antibody technology, one would design trials using the same pharmacokinetic guidelines which govern chemotherapy clinical trials. One would choose a target dose designed to be tolerable to normal tissues yet having maximal tumor destruction. The dose schedule would ensure that enough antibody penetrated into the tumor bed to achieve the therapeutic objectives. The route of administration should permit maximal exposure of the tumor to the antibody before systemic distribution.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Senior Investigator, National Cancer Institute – Navy Medical Oncology Branch, Clinical Oncology Program, Division of Cancer Treatment, National Institutes of Health, Bethesda, Maryland, USA.

Initial clinical trials, including our own institution's experience with T101 in cutaneous T-cell lymphoma, have promoted our understanding of these issues. In a Phase I study of T101 (a pan T-cell monoclonal antibody) while looking for appropriate dose, we discovered that higher doses (approximately 100 mg) were needed before monoclonal antibody could be recovered from biopsy specimens of the tumors. These higher doses were associated with systemic toxicity. The mouse immunoglobulin caused antigen-bearing cells to sludge in the pulmonary vasculature. The resulting side effects of wheezing, bronchospasm and urticaria could be prevented in part by antihistamines and by slowing the rate of immunoglobulin infusion. Since, in their native state, these antibodies were not effective therapeutically, even at their highest tolerable dose, they are no longer used alone. Other groups have confirmed that one must use 100 mg doses to target the tumor with antibodies.

The second issue was that of scheduling antibody. Again, we wished to choose a dose schedule that ensured adequate pharmacokinetic levels of the antibody, bearing in mind that the monoclonal antibody is a foreign protein and therefore immunogenic. In initial therapeutic trials of monoclonal antibodies, workers have reported that repeated injection of monoclonal antibody were associated with the human antimouse antibody response. While none of these reactions were fatal, several patients experienced anaphylaxis. It may be possible to offset this host immune response by such approaches as delivery by continuous infusion or by modifying host tolerance. More research is needed to explore further these scheduling issues.

The final concern is the route of antibody injection. When compared to intravenous administration of antibody, intralymphatic antibody administration markedly enhances the efficiency of antibody delivery to target tissues . We injected antibody subcutaneously into foot webs of patients with cutenous T-cell lymphoma while visualizing the regional lymphatics of the lower trunk. In addition to a two-log increase in per cent of dose recovered in target nodes, antibody given subcutaneously produced minimal cross reactivity with normal organs (an order of magnitide less uptake in liver and spleen than that associated with intravenous injection). While this route of administration has considerable merit, only a relatively few tumors involve regional lymphatics during a significant portion of their natural history. To explore this approach in a more clinically relevant setting, one could envision intralymphatic administration of antibody to enclosed visceral organs using fiberoptic instruments. In normal dogs, we have shown that intralymphatic administration antibody (via a bronchoscope into the bronchial airways) produces the same kind of kinetics as seen in tumor-bearing animals after subcutaneous antibody administration. It is possible that, in humans, this approach would have the same delivery advantage as subcutaneous injection of monoclonal antibody in patients with cutaneous lymphoma If so, imaging the mediastinal lymph nodes in patients with lung cancer might be of benefit.

Also monoclonal antibodies might be used for other therapeutic approaches such as to sequester vital growth factors that tumor cells require for their ongoing proliferation. Todaro and Sporn have postulated that tumor cells produce their own vital growth factors and thus achieve autonomous growth. We have developed a strategy whereby we can sequester a growth factor GRP, which is trophic for small-cell lung cancer, from the tumor by the use of the monoclonal antibody. There is evidence, both in vitro and in vivo, that this strategy is successful and is the basis for a new clinical effort in small-cell lung cancer patients.

In summary, therapeutic use of monoclonal antibodies is a fertile area of development. Clinical investigators are challenged to develop rational strategies to enhance control of cancer growth and then to catalyze the development of the appropriate reagents (including monoclonal antibodies) to best accomplish that control.

PROBLEM-KNOWLEDGE COUPLERS IN MEDICAL PROBLEM-SOLVING*

The Harold G. Vail Lecture

L.L. WEED, M.D.**, *Burlington, Vermont*

Solving a diagnostic or management problem in oncology presents the same basic challenges as in any other area of problem-solving. For example, if a middle-aged male appears with a suspicious finding on a chest x-ray, several questions must be asked and on physical examination specific things checked for. Then the results should be used in a consistent and rigorous manner to choose among procedures (biopsies, scans, cytology, etc.), to further clarify the situation.

A clinician may make mistakes when he cannot recall all the options for action (assuming he once knew them all), or fails to elicit from the patient the crucial details that help him to select among options. Also the number of options and details about the patient may be so great and the time available so short that the clinician is overwhelmed and never carries out a highly organized and disciplined matching between details about the patient and the appropriate course of action.

Medical education, postgraduate courses and conferences such as this all operate on the premise that the unaided human mind, if properly educated, can recall and process large number of variables in complex clinical situations without slipping and making serious mistakes. We have ignored the literature of psychology that warns about the limitations of the human mind, and have stubbornly persisted in our failed approaches. We have just kept on memorizing, regurgitating, credentialing, and forgetting. We continue to misread the message our mistakes are trying to send.

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*Abstract of a paper presented at the 24th OCTRF Clinical Conference held in Ottawa on October 7, 1986.

**Professor Emeritus of Medicine, University of Vermont, Burlington, Vermont, USA.

Some of the traps the unaided mind will fall into are:

- The unaided mind will start generating hypotheses in the earliest moments of encounters with patients and thereby prematurely bias the remaining steps in the search for data.
- The mind will limit the number of hypotheses it generates to a number smaller than is appropriate to the problem.
- The mind will generate hypotheses that are more general than the data actually allow. Crucial findings in a data base will be disregarded. Often it will dismiss significant historical facts as mere "clinical suspicion", and pay attention instead to expensive tests that are far less sensitive and specific. As Wason and Johnson-Laird have pointed out: "When the individual mind's logical ability is restricted, it will operate within heuristic or "hit-or-miss" procedures which do not guarantee a solution".
- The mind, having neglected to use the power of low risk, simple, "easy-to-obtain" data in the aggregate, tends to proceed prematurely to expensive high-risk procedures.
- The mind will underestimate the complexity of problems and it will overinterpret the data it does collect. It will indulge in the categorial reasoning of the expert, which can lead to the ordering of laboratory tests that are off-target. This, as Galen has said, is the main reason why many tests lack specificity and sensitivity.
- The mind will take probablistic information based on studies of large populations, and let it supercede highly improbable but correct information from a unique patient, often getting that particular patient into trouble. Also it applies literature-based prevalence data in many of its calculations, which is entirely inappropriate to the population to which the patient belongs.

We like to believe as Wason and Johnson-Laird have said, that the educated human mind is capable of thinking in terms of propositions which take into account the possible and the hypotherical, and that this mind will be able to isolate the variables in the problem and subject them to combinatorial analysis which nicely exhausts the possibilities. However, much research shows that the mind cannot do this consistently or reliably. Therefore we ought to design systems that extend the human mind, just as we use x-rays to extend human vision for lesions within the body that the unaided vision cannot see. The Problem-Knowledge Coupler System was designed to aid the human mind in combinatorial reasoning at the time of problem-solving.

The following example shows how it works.

The patient with the suspicious lung lesion, referred to above, would be cared for in an environment where the patient and the provider have a microcomputer available. It would function as follows:

After choosing the proper problem, a display (Fig. 1) will appear on the screen of the microcomputer. One reads the display and makes a choice by typing the number in front of the desired option. In this case, let us type number 1, which produces the Relevant History (Fig. 2); again, choices are made by typing

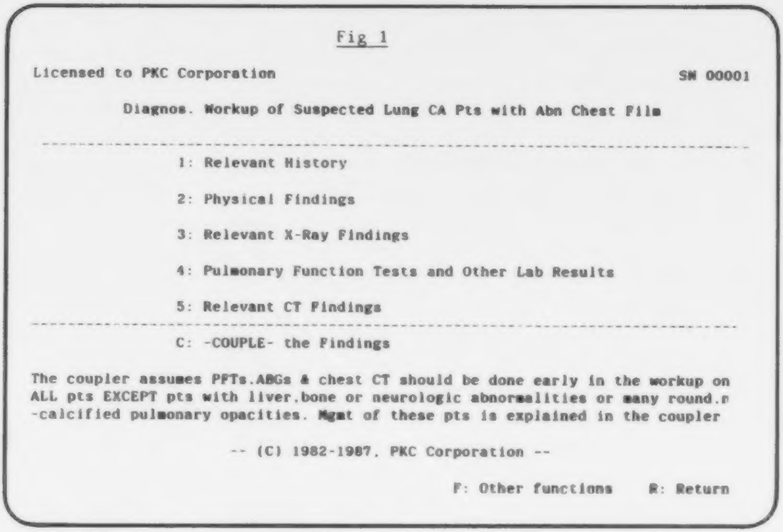

Fig 1

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Licensed to PKC Corporation                                        SN 00001

         Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
 ---------------------------------------------------------------------------
                 1: Relevant History

                 2: Physical Findings

                 3: Relevant X-Ray Findings

                 4: Pulmonary Function Tests and Other Lab Results

                 5: Relevant CT Findings
 ---------------------------------------------------------------------------
                 C: -COUPLE- the Findings

The coupler assumes PFTs.ABGs & chest CT should be done early in the workup on
ALL pts EXCEPT pts with liver.bone or neurologic abnormalities or many round.n
-calcified pulmonary opacities. Mgmt of these pts is explained in the coupler

                   -- (C) 1982-1987. PKC Corporation --

                                          F: Other functions    R: Return
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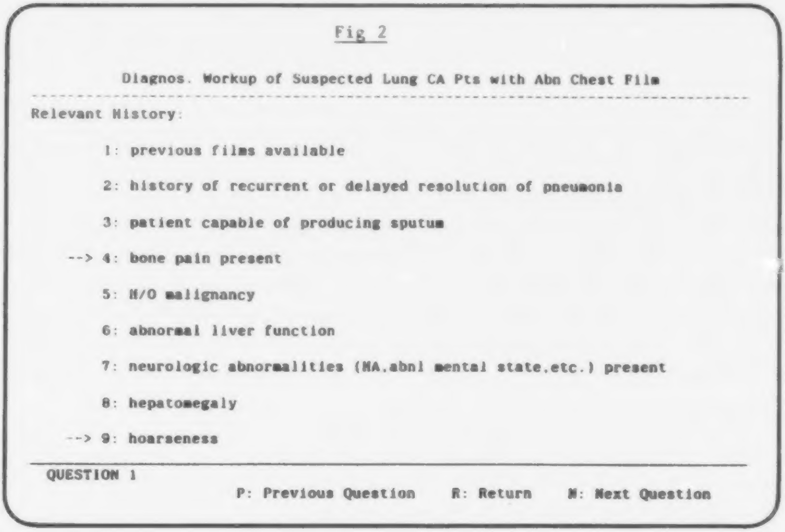

Fig 2

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         Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
 ---------------------------------------------------------------------------
Relevant History:

           1: previous films available

           2: history of recurrent or delayed resolution of pneumonia

           3: patient capable of producing sputum

       --> 4: bone pain present

           5: H/O malignancy

           6: abnormal liver function

           7: neurologic abnormalities (HA.abnl mental state.etc.) present

           8: hepatomegaly

       --> 9: hoarseness
 ___________________________________________________________________________
  QUESTION 1
                    P: Previous Question    R: Return    N: Next Question
```

the number in front of the appropriate text, in this case, numbers 4 and 9. An arrow appears to show the choice has been made. If the user changes his mind, he types the number again and the arrow disappears. After making all the appropriate choices from this display, the user looks for guidance at the bottom of the screen and sees N: Next Question. He types the letter "N" and Fig. 3 appears. In a similar fashion one progresses through Figs. 4, 5 and 6, making choices as one goes. After Fig. 6, the user is taken back to Fig. 1, where one could choose sequences 4 and 5 and give relevant pulmonary function studies or CT findings. Let us assume we have not done those but would like to know the significance of our choices thus far. This is accomplished by typing the letter "C" for "COUPLE the Findings". Immediately Fig. 7 appears. This is a summary of the positive findings. The user may then make the choice at the bottom of the screen "M" for "Management Options, and Fig. 8 appears. One can study each of these options by typing the number in front of it. Fig. 9 is a review of all the management options, the patient's findings, which elicited each, and the comments on each that help the user plan the next steps in the work-up.

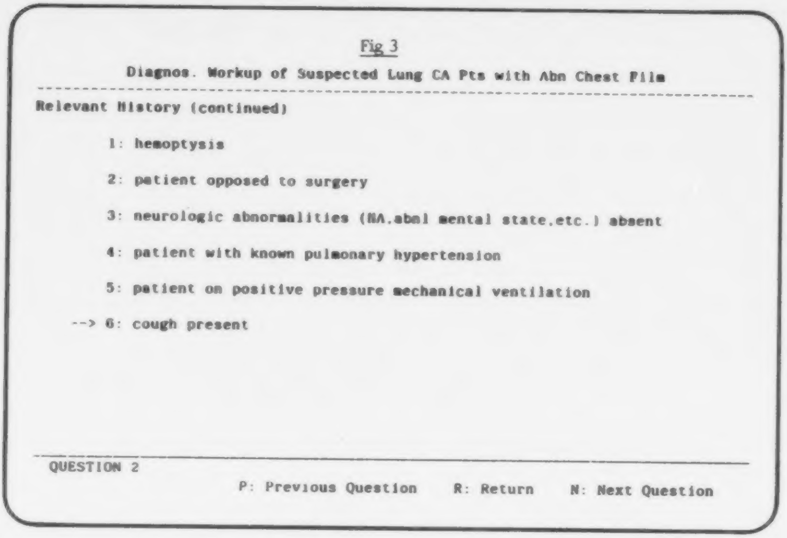

Fig 3

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            Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
-------------------------------------------------------------------------------
Relevant History (continued)

          1: hemoptysis

          2: patient opposed to surgery

          3: neurologic abnormalities (NA,abnl mental state,etc.) absent

          4: patient with known pulmonary hypertension

          5: patient on positive pressure mechanical ventilation

      --> 6: cough present




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 QUESTION 2
                        P: Previous Question    R: Return    N: Next Question
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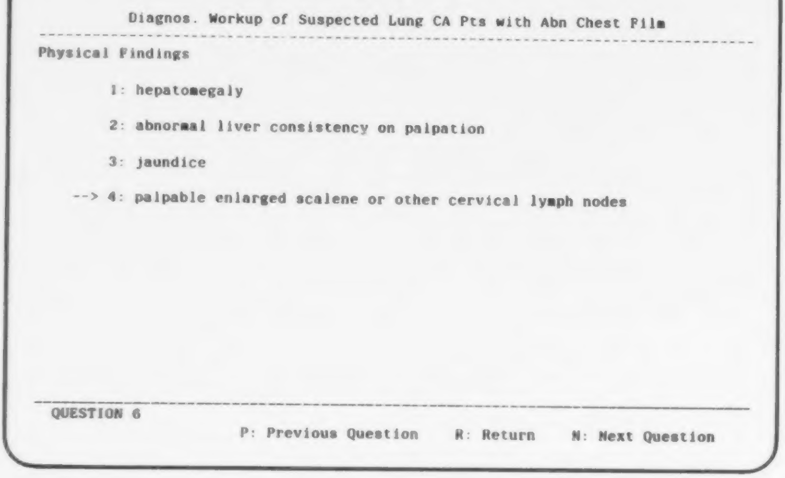
Fig 4



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          Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
--------------------------------------------------------------------------------
Physical Findings

           1: hepatomegaly

           2: abnormal liver consistency on palpation

           3: jaundice

       --> 4: palpable enlarged scalene or other cervical lymph nodes





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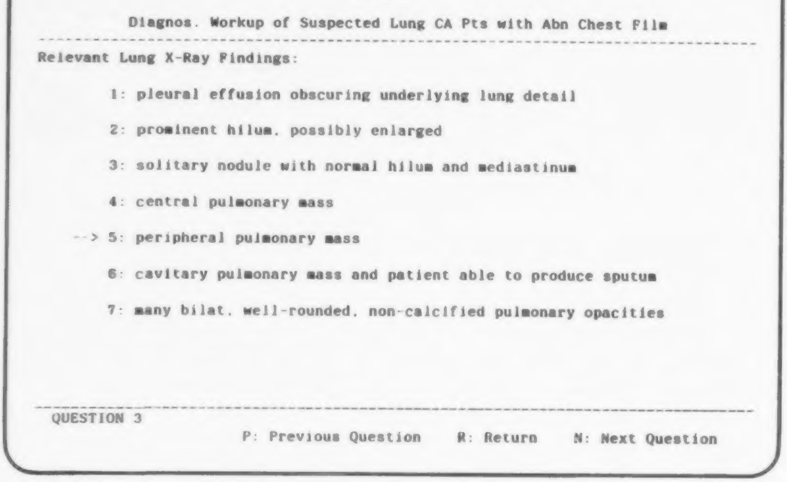
  QUESTION 6
                         P: Previous Question    R: Return    N: Next Question
```

Fig 5



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          Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
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Relevant Lung X-Ray Findings:

           1: pleural effusion obscuring underlying lung detail

           2: prominent hilum, possibly enlarged

           3: solitary nodule with normal hilum and mediastinum

           4: central pulmonary mass

       --> 5: peripheral pulmonary mass

           6: cavitary pulmonary mass and patient able to produce sputum

           7: many bilat. well-rounded, non-calcified pulmonary opacities


--------------------------------------------------------------------------------
  QUESTION 3
                         P: Previous Question    R: Return    N: Next Question
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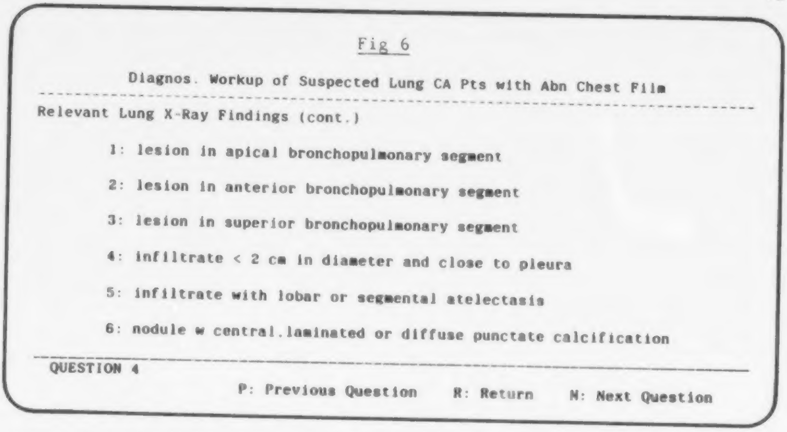

Fig 6

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          Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film
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Relevant Lung X-Ray Findings (cont.)

        1: lesion in apical bronchopulmonary segment

        2: lesion in anterior bronchopulmonary segment

        3: lesion in superior bronchopulmonary segment

        4: infiltrate < 2 cm in diameter and close to pleura

        5: infiltrate with lobar or segmental atelectasis

        6: nodule w central.laminated or diffuse punctate calcification
--------------------------------------------------------------------------------
 QUESTION 4
                        P: Previous Question    R: Return    N: Next Question
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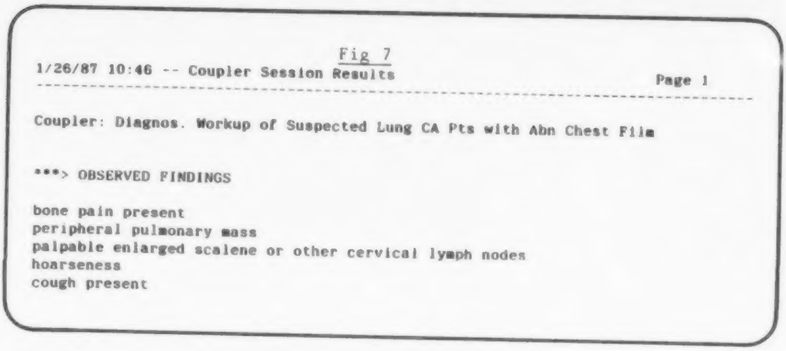

Fig 7

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1/26/87 10:46 -- Coupler Session Results                              Page 1
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Coupler: Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film


***> OBSERVED FINDINGS

bone pain present
peripheral pulmonary mass
palpable enlarged scalene or other cervical lymph nodes
hoarseness
cough present
```

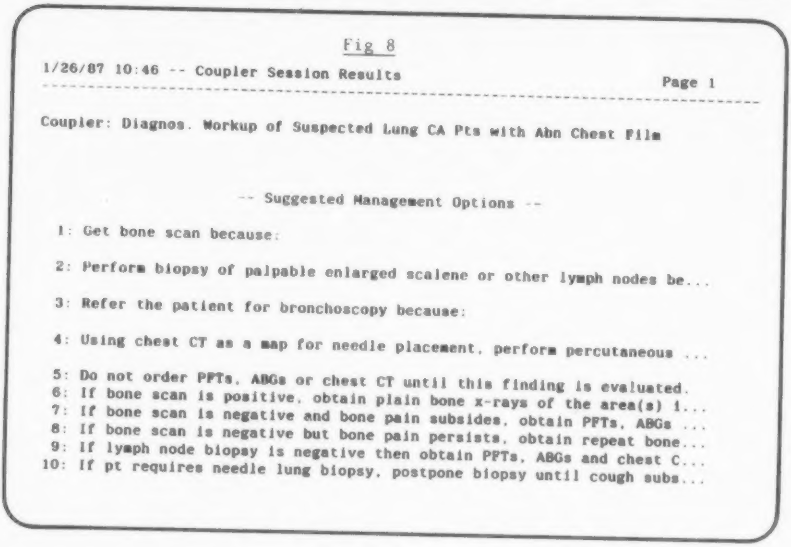

Fig 8

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1/26/87 10:46 -- Coupler Session Results                              Page 1
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Coupler: Diagnos. Workup of Suspected Lung CA Pts with Abn Chest Film



                     -- Suggested Management Options --

 1: Get bone scan because:

 2: Perform biopsy of palpable enlarged scalene or other lymph nodes be...

 3: Refer the patient for bronchoscopy because:

 4: Using chest CT as a map for needle placement, perform percutaneous ...

 5: Do not order PFTs, ABGs or chest CT until this finding is evaluated.
 6: If bone scan is positive, obtain plain bone x-rays of the area(s) i...
 7: If bone scan is negative and bone pain subsides, obtain PFTs, ABGs ...
 8: If bone scan is negative but bone pain persists, obtain repeat bone...
 9: If lymph node biopsy is negative then obtain PFTs, ABGs and chest C...
10: If pt requires needle lung biopsy, postpone biopsy until cough subs...
```

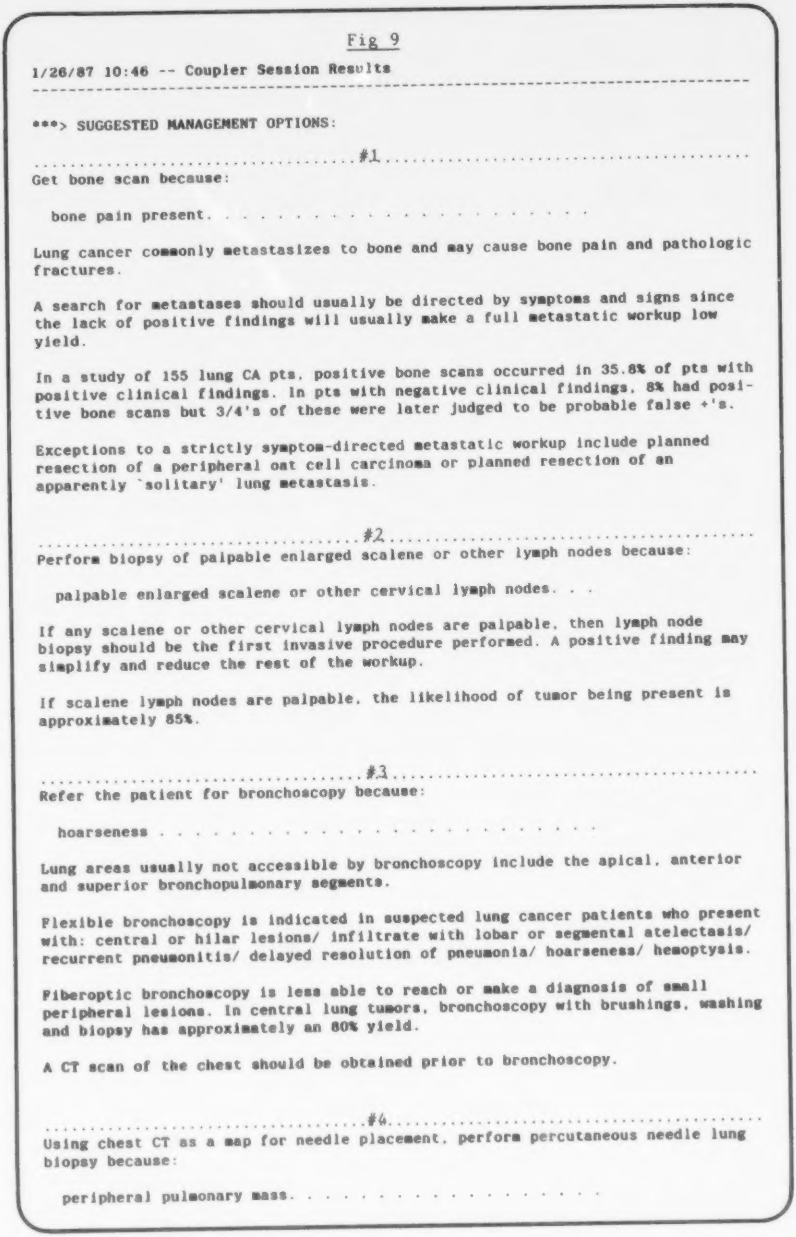

Fig 9

```
1/26/87 10:46 -- Coupler Session Results
---------------------------------------------------------------------

***> SUGGESTED MANAGEMENT OPTIONS:

.................................#1......................................
Get bone scan because:

  bone pain present. . . . . . . . . . . . . . . . . . . . . . . .

Lung cancer commonly metastasizes to bone and may cause bone pain and pathologic
fractures.

A search for metastases should usually be directed by symptoms and signs since
the lack of positive findings will usually make a full metastatic workup low
yield.

In a study of 155 lung CA pts, positive bone scans occurred in 35.8% of pts with
positive clinical findings. In pts with negative clinical findings, 8% had posi-
tive bone scans but 3/4's of these were later judged to be probable false +'s.

Exceptions to a strictly symptom-directed metastatic workup include planned
resection of a peripheral oat cell carcinoma or planned resection of an
apparently `solitary' lung metastasis.


.................................#2......................................
Perform biopsy of palpable enlarged scalene or other lymph nodes because:

  palpable enlarged scalene or other cervical lymph nodes. . .

If any scalene or other cervical lymph nodes are palpable, then lymph node
biopsy should be the first invasive procedure performed. A positive finding may
simplify and reduce the rest of the workup.

If scalene lymph nodes are palpable, the likelihood of tumor being present is
approximately 85%.


.................................#3......................................
Refer the patient for bronchoscopy because:

  hoarseness . . . . . . . . . . . . . . . . . . . . . . . . .

Lung areas usually not accessible by bronchoscopy include the apical, anterior
and superior bronchopulmonary segments.

Flexible bronchoscopy is indicated in suspected lung cancer patients who present
with: central or hilar lesions/ infiltrate with lobar or segmental atelectasis/
recurrent pneumonitis/ delayed resolution of pneumonia/ hoarseness/ hemoptysis.

Fiberoptic bronchoscopy is less able to reach or make a diagnosis of small
peripheral lesions. In central lung tumors, bronchoscopy with brushings, washing
and biopsy has approximately an 80% yield.

A CT scan of the chest should be obtained prior to bronchoscopy.


.................................#4......................................
Using chest CT as a map for needle placement, perform percutaneous needle lung
biopsy because:

  peripheral pulmonary mass. . . . . . . . . . . . . . . . . . .
```

Fig 9 (contd)

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1/26/87 10:46 -- Coupler Session Results.
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Indications for needle lung biopsy in suspected lung cancer patients include:
peripheral lesion, infiltrates with diameter <2 cm close to pleura, apical le-
sion(s), mediastinal lesion after bronchoscopy unsuccessful in making diagnosis.

Indications for needle lung biopsy in solitary pulmonary nodule include: patient
refusal of open biopsy/ medical contraindications to open biopsy/ hx of pre-
existing malignancy outside of the chest (in which nodule may be a metastasis).

Needle lung biopsy has approximately 90% accuracy, but it may cause more
complications than bronchoscopy.  Complications include PNEUMOTHORAX, DEATH,
hemorrhage, hemoptysis, and tumor implantation.

Needle lung biopsy is best suited for small peripheral lesions and areas not
readily accessible to bronchoscopy such as the apical, anterior and superior
bronchopulmonary segments.

Contraindications to needle lung biopsy include abnormal coagulation or bleeding
tendencies. Patients receiving heparin but with otherwise normal clotting can
usually undergo needle lung biopsy if heparin is stopped and protamine is given.

Poor PFTs and arterial blood gases (PaO2 <60mm Hg and elevated PaCO2) usually
contraindicate needle lung biopsy unless there are compelling reasons and the
likelihood of pneumothorax is very small.

The combination of markedly abnormal arterial blood gases and severe obstructive
airway disease ( < 50% of predicted flow rates) is also usually a contraindica-
tion to needle lung biopsy.

Bullous lung disease is only a relative contraindication to needle lung biopsy
since a resulting pneumothorax can be satisfactorily treated in a patient with
adequate pulmonary reserve.

Additional contraindications to needle lung biopsy include pulmonary hyperten-
sion and positive pressure mechanical ventilation.(Mechanical ventilation in-
creases the risk of air embolism.)

Chest CT should be obtained before needle lung bx to plan best approach.Actual
needle placement can be done under fluoroscopic or,in some cases,CT guidance.
Combining both modalities will facilitate safe and accurate biopsy sampling.


.................................#5........................................
Do not order PFTs, ABGs or chest CT until this finding is evaluated.

  bone pain present. . . . . . . . . . . . . . . . . . . . . . .
  palpable enlarged scalene or other cervical lymph nodes. . .

Patients with this/these finding(s) may demonstrate metastatic disease and thus
be non-resectable thereby making PFTs and chest CT unnecessary (unless needle
biopsy for diagnosis is still needed).


.................................#6........................................
If bone scan is positive, obtain plain bone x-rays of the area(s) in question.

  bone pain present. . . . . . . . . . . . . . . . . . . . . . .

Besides bone metastases, other causes of positive bone scans include soft tissue
calcification, healing fracture, bone infarct, benign bone tumor, hyperostosis,
degenerative arthrosis and osteoarthritis.
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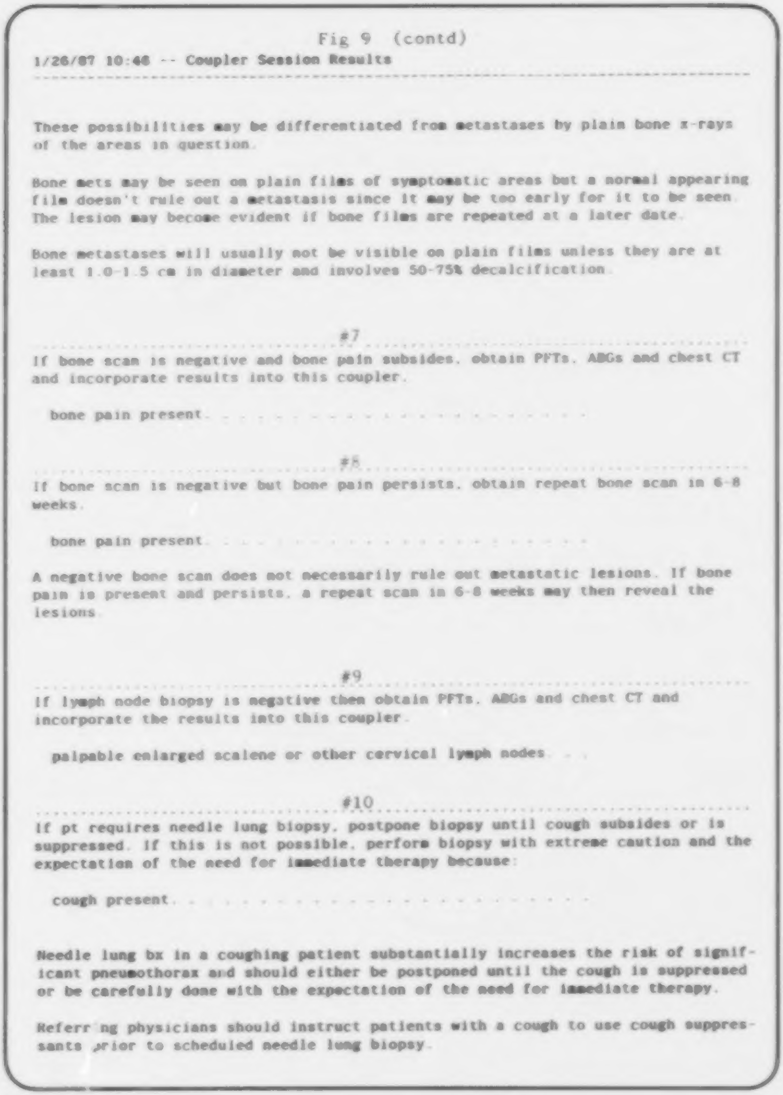

Fig 9 (contd)

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1/26/87 10:46 -- Coupler Session Results
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These possibilities may be differentiated from metastases by plain bone x-rays
of the areas in question.

Bone mets may be seen on plain films of symptomatic areas but a normal appearing
film doesn't rule out a metastasis since it may be too early for it to be seen.
The lesion may become evident if bone films are repeated at a later date.

Bone metastases will usually not be visible on plain films unless they are at
least 1.0-1.5 cm in diameter and involves 50-75% decalcification.


                                     #7
................................................................................
If bone scan is negative and bone pain subsides, obtain PFTs, ABGs and chest CT
and incorporate results into this coupler.

  bone pain present. . . . . . . . . . . . . . . . . . . . . .

                                     #8
................................................................................
If bone scan is negative but bone pain persists, obtain repeat bone scan in 6-8
weeks.

  bone pain present. . . . . . . . . . . . . . . . . . . . . .

A negative bone scan does not necessarily rule out metastatic lesions. If bone
pain is present and persists, a repeat scan in 6-8 weeks may then reveal the
lesions.


                                     #9
................................................................................
If lymph node biopsy is negative then obtain PFTs, ABGs and chest CT and
incorporate the results into this coupler.

  palpable enlarged scalene or other cervical lymph nodes. . .

                                     #10
................................................................................
If pt requires needle lung biopsy, postpone biopsy until cough subsides or is
suppressed. If this is not possible, perform biopsy with extreme caution and the
expectation of the need for immediate therapy because:

  cough present. . . . . . . . . . . . . . . . . . . . . . . .

Needle lung bx in a coughing patient substantially increases the risk of signif-
icant pneumothorax and should either be postponed until the cough is suppressed
or be carefully done with the expectation of the need for immediate therapy.

Referring physicians should instruct patients with a cough to use cough suppres-
sants prior to scheduled needle lung biopsy.
```

With this simple tool we have accomplished the following:

1. An assurance to patients that all the crucial information is covered without depending upon the provider's memory to recall all the right questions and the significance of the positive answers to each.
2. Immediately typed copies are available so that all concerned can make a careful study of options without having any of the relevant points obscured by premature hypotheses or individual biases.
3. The ability to incorporate new approaches promptly and easily as they appear in the field. Thus everyone can be kept up-to-date regardless of what he reads and regardless of any limitations on human capacities to recall and process large numbers of variables at the time of action.

The "Editor" for building and revising or adding to Couplers is easy to learn and use and requires no computer background. The emphasis is on the medical knowledge involved. The knowledge in this coupler was organized by Drs. Peter Dietrich and Basil Grieco of the Department of Radiology of the University of Vermont. Every choice is referenced and medical knowledge can now be coupled to patients' needs without the "voltage drop" produced in the past by faulty premises in medical education.

SUGGESTED READING

Wason PC, Johnson-Laird P: Psychology of reasoning. Cambridge, Mass.: Harvard University Press, 1972.

Kern L, Doherty ME: Pseudodiagnosticity in an idealized medical problem-solving environment. *J Med Educ* 1982; **57:** 100.

Detmer DE, Fryback PG, Gassnek K: Heuristics and biases in medical decision-making. *J Med Educ* 1978; **53:** 682.

Tversky A, Kahneman P: Judgement under uncertainty: Heuristics and biases. *Science* 1974; **185:** 1124.

Weed CC: Problem-knowledge couplers: Philosophy, use and interpretation 1982; (a concept paper written for the PKC Corporation, 10 Mary St., South Burlington, Vermont 05401).

Weed LL, Hertzberg RY: The use and construction of problem-knowledge couplers, the knowledge-coupler editor, knowledge networks, and the problem-oriented medical record for the microcomputer. Proceedings of the Seventh Symposium on Computer Applications in Medical Care, published by IEEE, 1983: 831.

Weed LL: Knowledge coupling, medical education and patient care. *Crit Rev Med Informatics* 1986; **1:** 55.

REGIONAL CANCER CENTRES

REGIONAL CANCER CENTRES

The Ontario Cancer Foundation was established in 1943 by an Act of the Ontario Legislature to conduct a program of research, diagnosis and treatment in cancer. The Foundation works in three fields: service, research and education. From its inception, the Foundation has accepted responsibility for:

– the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or special facilities; and

– the maintenance and operation hostels in connection with its treatment centres.

The Foundation also has the most important duty of co-ordinating facilities for cancer treatment and ensuring the adequate reporting of cases and the recording and compilation of data.

The Foundation with its eight Regional Cancer Centres -- Hamilton, Kingston, London, Ottawa, Sudbury, Thunder Bay, Toronto-Bayview, and Windsor -- provide facilities for undergraduate and postgraduate study, training of technical personnel, and research fellowships to increase our knowledge about cancer.

The Foundation is distinct from but co-operates with the Ontario Cancer Institute incorporating the Princess Margaret Hospital in the investigation and treatment of cancer and works closely with the Canadian Cancer Society Ontario Division.

The Foundation hopes that *Cancer in Ontario* will assist the practising physician in some of the following ways:

– help him/her become familiar with the various services of the Foundation and its Centres;

– encourage effective patterns of referral and to promote efficient geographical use of the Regional Cancer Centres;

– encourage the individual physician to consult informally with staff members at the Regional Cancer Centre;

– make the resources of the Foundation more widely available to the people of Ontario by increasing the number of contacts between physicians, particularly those outside metropolitan areas, and the OCI/PMH and the Foundation's Regional Cancer Centres.

We urge any physician who reads *Cancer in Ontario* to make suggestions concerning the improvement of cancer control in Ontario. These may be transmitted to the Director of the nearest Regional Cancer Centre or sent directly to the Executive Director, Dr. J.W. Meakin. The Directors of the Regional Cancer Centres may be contacted as follows:

OCTRF Head Office
Executive Director – Dr. J.W. Meakin
7 Overlea Blvd.
Toronto, Ontario M4H 1A8
Telephone: (416)423-4240

Hamilton Regional Cancer Centre
Director – Dr. W.M. Hryniuk
Henderson General Hospital
711 Concession Street
Hamilton, Ontario L8V 1C3
Telephone: (416)387-9495

Kingston Regional Cancer Centre
Director – Dr. A.D. Ginsburg
Kingston General Hospital
King Street West
Kingston, Ontario K7L 2V7
Telephone: (613)544-2630

London Regional Cancer Centre
Director Elect – Dr. L. Levin
Victoria Hospital
391 South Street
London, Ontario N6A 4G5
Telephone: (519)679-9890

Northeastern Ontario
Oncology Program
Director – Dr. R.E.T. Corringham
Laurentian Hospital
41 Ramsey Lake Road
Sudbury, Ontario P3E 5J1
Telephone: (705)522-2200

Ottawa Regional Cancer Centre
Director – Dr. G.E. Catton
Civic Hospital Division
190 Melrose Avenue
Ottawa, Ontario K1Y 4K7
Telephone: (613)725-6300

General Hospital Division
501 Smyth Road
Ottawa, Ontario K1G 8L6
Telephone: (613)737-8715

Thunder Bay Regional Cancer Centre
Director – Dr. J.F. Kotalik
General Hospital of Port Arthur
290 Munro Street
Thunder Bay, Ontario P7A 7T1
Telephone: (807)343-1610

Toronto-Bayview Regional
Cancer Centre
Director – Dr. R.D.T. Jenkin
Sunnybrook Medical Centre
2075 Bayview Avenue
Toronto, Ontario M4N 3M5
Telephone: (416)488-5801

Windsor Regional Cancer Centre
Director – Dr. G.C.K. Mok
Metropolitan General Hospital
2220 Kildare Road
Windsor, Ontario N8W 2X3
Telephone: (519)253-5253

OCF

HAMILTON REGIONAL CANCER CENTRE

HENDERSON GENERAL HOSPITAL

Director:

W.M. Hryniuk, M.D.

Radiation Oncologists:

V.R. Basrur, Ph.D., M.D.
D.I. Hodson, M.B.,B.Ch.
C.R. Johanson, M.D.
W. Muirhead, M.B.,Ch.B.
I.Z. Strautmanis, M.D.
A.A.M. Tadros, M.B.,B.Ch.

Medical Oncologists:

A. Arnold, M.B.,B.S.
G.P. Browman, M.D.
E. Chouinard, M.D.
A.T. Figueredo, M.D.
M.N. Levine, M.D.
P.B. McCulloch, M.D.
A.J. Neville, M.B.,Ch.B.

Physicists:

C. Kwok, Ph.D.
M. Patterson, Ph.D.
V.G. Peters, B.Sc.
R.H. Price, B.Eng.
B.C. Wilson, Ph.D.
D. Wyman, Ph.D.

Clinical Assistants:

M.D.E. Goodyear, M.B.,B.S.
M.E. McBride, M.D.
C. Jones, M.D.
E. Latimer, M.D.
A. Monkhouse, M.D.
D. Nicholson, M.B.,B.Ch.
C.L. Tanser, M.D.

Career Scientists:

W.P. Jeeves, Ph.D.
G. Singh, Ph.D.

Administrator:

C.E. Squires

Business Office Manager:

C.F. Freeman, R.I.A.

Senior Radiotherapy Technician:

B.J. Walker, R.T.

Nurse Administrator:

H.B. Porter, B.N.Sc.

Cancer Information Services:

B. Rigby, B.Sc.N., M.H.Sc.

Manager of Health Records:	**Lodge Supervisor:**
D. Armstrong	C. Stewart, R.N.

1986 was a year of continuing changes at the Hamilton Regional Cancer Centre. Dr. Charles Catton of Radiation Oncology Department left us to join the staff of the Toronto-Bayview Centre. Dr. D.I. Hodson from Winnipeg joined the department in September.

Dr. Edward Chouinard, who was appointed to the medical oncoloncology staff, is working at the outreach clinics at McMaster University Medical Centre and St. Joseph's Hospital.

In May, Dr. George Browman resigned as Head of Research for the Centre. Dr. Brian Wilson has assumed the dual role of Head of Medical Physics and of Research.

Janet Craven, R.N. has been appointed Assistant Nurse Administrator for the Centre.

The many changes in the physical plant and renovations in progress are interim measures to relieve our current overcrowding.

Completion of the third floor of Lakeview Lodge, provided accommodation for the Business Office and the Departments of Medical Oncology and Clinical Trials. Renovations were undertaken to relocate the superficial machine and to accommodate the new Philips simulator, which will be installed in January 1987. Facilities are also being prepared for the newly approved Cobalt machine.

Plans are underway to put trailers in the parking area north of the Centre to meet our current space needs. These trailers will provide essential office, conference room and storage space, and will accommodate computer services and the planning department.

The major focus of 1986 has been planning for the new facility. Mr. Robert Price is continuing to co-ordinate planning activities. Construction is scheduled to begin in early 1988.

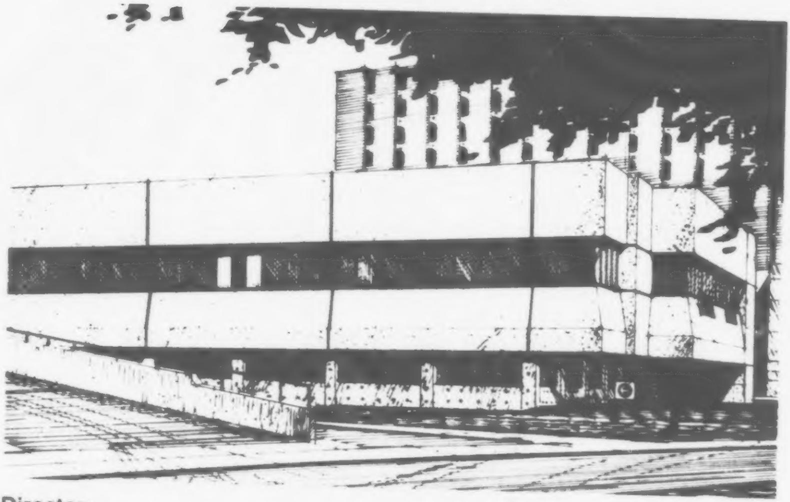
Medical and nursing staff continue their involvement in clinical trials in conjunction with the OCOG, MRC, Leukemia Intergroup and others. Dr. Andrew Arnold has received a Ministry of Health prevention grant to study the effect of etretinate on squamous metaplasia in smokers.

Basic research projects continue and the clinical physics staff are involved in ongoing programs of research and develpment.

B. Rigby, B.Sc.N., M.H.Sc.
Co-ordinator, Cancer Information Services

KINGSTON REGIONAL CANCER CENTRE

KINGSTON GENERAL HOSPITAL



Director:

A.D. Ginsburg, M.D.

Radiation Oncologists:

P.F. Dixon, M.B.,B.S.
P.J. Froud, M.B.,Ch.B.
V. Kraus, M.D.
W.J. Mackillop, M.B.,Ch.B.

Medical Oncologists:

B.J. Campling, M.D.
E.A. Eisenhauer, M.D.
P.R. Galbraith, M.D.
J.L. Pater, M.D.

Clinical Assistants:

M.D. Mulligan, M.R.C.S., L.R.C.P.
D.C. Pross, M.D.
W. Shelley, M.D.

Career Scientists:

S.P.C. Cole, Ph.D.
J.C. Kennedy, M.D.

Physicists:

J. Robins, M.A.
P.C. Shragge, Ph.D.

Honorary Medical Consultant:

R.C. Burr, M.D.

Administrator:

D.H.D. Steacy, B.A.

Head Nurse/Chief Technician:

E.M. Bolster, Reg.N., R.T.(T)

Social Service Nurses:

R. Crafts, Reg.N.
C. Keith, Reg.N.

Manager of Health Records:

R.S. Walker

Lodge Supervisor:

D. Broeders, Reg.N.

1986 has seen an exciting continuation of research activity in oncology in the Kingston Centre. Drs. Susan Cole, Barbara Campling, and William Mackillop are developing a strong thematic program in research related to drug resistance; and in the near future they will be joined in this activity by Dr. James Gerlach. Dr. James Kennedy continues his innovative approaches to treatment in cancer and, in this regard, has forged links in Scotland and with the Royal Military College in Kingston. Dr. William Mackillop is spearheading a number of interesting studies relating to informed consent and supportive and emotional care of patients. Under Dr. J. Pater's leadership, the NCIC group remains active and provides a variety of studies. There is increasing collaboration with faculty in other departments and pathology, biochemistry, biology, immunology, psychiatry, urology and surgery have all participated vigorously with oncology. A weekly seminar program under the able direction of Drs. Wm. Mackillop, B. Campling and B. Elliot deals predominantly with molecular genetics. This and similar activities have brought increasing interaction in the Centre among faculty and students from several disciplines and has proved highly successful both in content and in promoting a collaborative spirit. This year through the creation of an endowed chair in cancer research -- the Stauffer Chair -- Queen's University has been particularly supportive of research in oncology.

The eclectic nature of oncology has received official recognition from Queen's University, the Kingston General Hospital and the Hotel Dieu Hospital; all three centres have established departments of oncology. This development reflects the close working relationships between the radiation oncologists, the medical oncologists and the basic scientists in the department. We are also fortunate in having the firm support of a large number of individuals from other departments. We are pleased to announce that Drs. John Carmichael in the Department of Gynecology, Stephen Hall in the Department of Otolaryngology and Bruce Elliot in the Department of Pathology have accepted cross-appointments in our department.

Two members of our Centre have become "heads" of other departments at Queen's University this year -- Drs. Hugh Pross is now Chairman of the Department of Microbiology and Immunology, and Joe Pater is Chairman of the Department of Community Health and Epidemiology. We wish them both well and are certain that these appointments will ensure continued co-operation among our various departments.

In the educational sphere, Dr. Peter Dixon has built on the legacy of Dr. Peter Froud and the residency training program in radiation oncology has grown from strength the strength. It has been enhanced further through the co-operation of the Family Medicine Department which now rotates a junior resident through the Centre.

1986 had more than a tinge of sadness as Miss Margie Bolster will retire in February 1987 after 40 years with the OCTRF and with the Kingston Centre. In essence, she IS the centre.

A.D. Ginsburg, M.D., F.R.C.P.(C)
Director

LONDON REGIONAL CANCER CENTRE

VICTORIA HOSPITAL

LONDON CLINIC
THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Director:

H. Bush, M.B.,B.S., Ph.D.

Radiation Oncologists:

W.E.C. Allt, M.D.
P. Banerjee, M.B.,B.S.
A. Cheung, M.D.
P.J. Corbett, M.B.,B.S.
A.R. Dar, M.B.,B.S.
J.A. Gilchrist, M.B.,B.S.
J.A. Hammond, M.D.

Medical Oncologists:

V. Bramwell, M.B.,B.S.
G. Cairncross, M.D.
W.I. Kocha, M.D.
L. Levin, M.B.,Ch.B.
R.C. Lohmann, M.D.
D. Macdonald, M.D.
J. Skillings, M.D.
A. Smith, M.D.

Physicists:

D.J. Dawson, Ph.D.
K.S. Chang, Ph.D.
J. Schoeder, M.Sc.

Career Scientists:

A. Chambers, Ph.D.
J. Harris, Ph.D.
W.R. Inch, Ph.D.
D.J. Koropatnick, Ph.D.

Terry Fox Fellows:

J.D. Awde, D.D.S.
A. Tuck, M.D.

Administrator:

M.J. Morrison, M.P.A.

Business Manager:

T. Norris, B.Comm.

Nursing Co-ordinator:

W. Gillis, B.Sc.N.

Senior Radiotherapy Technologist:

U. Ardy, R.T.T.

Social Worker:

A. Sawarna, M.S.W.

Manager of Health Records:

D.G.E. Ross, C.C.H.R.A.

Lodge Supervisor:

R. Emery, B.Sc.N.

In many areas of its regional activities, the London Regional Cancer Centre has had a prosperous 1986. The planning process for the new facility was completed in August. At a ceremony on the new Westminster site, the Premier, the Hon. David Peterson, "broke ground" in September to initiate the construction phase. The new facility is expected to be open and ready for occupation in the spring of 1988. A number of staff changes occurred in 1986. Dr. James Gilchrist resigned, returning to Ethiopia to continue his established contribution to third-world, health-care development. Dr. Wm. Allt retired after a career as a staff radiation oncologist both at the OCI/PMH and, most recently, at the London Centre. Nursing co-ordinator Mary Jane Hodsman resigned to pursue full-time doctoral studies at the University of Western Ontario having set the Department of Nursing on a firm pathway towards comprehensive, primary care, oncology nursing. The Centre's basic and clinical scientisits have been recognized in North America and Europe this year through their invited participation at many international workshops and symposia.

The Centre has continued to prepare for full accreditation with the Canadian Council of Hospital Accreditation. As we bring ourselves in line with other hospitals and our sister clinics in the province, the accreditation of this large ambulatory facility will provide a new experience for the Council.

Our large outreach activity in Southwestern Ontario was further expanded when the Minister of Health announced funding for a linked ambulatory community oncology unit at the St. Thomas-Elgin Hospital in St. Thomas.

In the Terry Fox training program Dr. Doug Awde completed his studies on cell-cycle regulation and earned an M.Sc. in pharmacology. He returns to the University of Western Ontario for further medical studies. On completion of these studies, he will be in a unique position to develop the field of dental oncology in the London Centre and the surrounding region. The newest Terry Fox Fellow, Dr. Alan Tuck, joins Dr. Ann Chambers to work in the field of tumor progression and metastasis.

Caring and curing have become the watchwords of the London Centre. While we continue to pioneer new clinical and basic approaches to the optimal management of established cancer, we have opened a second "front" in early diagnosis and prevention. Our participation in the National Breast Screening program continues, but Dr. Leslie Levin and Mrs. Diane Goettler have initiated a new pilot program to evaluate the relationship between diet and breast cancer. This study will investigate the abnormal release of certain peptide hormones in response to a high-fat test meal in both breast cancer patients and their healthy counterparts.

Care has become an increasing focus of this Centre's activities through the department of social work and the palliative care team. Physicians, nurses, radiation technologists and social workers have received workshop training in the techniques of psychosocial counselling and intervention with the survivals.

In February 1986, Dr. Haydn Bush resigned as director of the London Regional Cancer Centre; this change to take effect June 30, 1987. He will enrol in the psychiatry residency program of Dalhousie University in Halifax for further training; at its conclusion, Dr. Bush will come back to oncology with a strong psychosocial focus.

In radiation oncology we anticipate the imminent arrival of Dr. Leon Houghton from the Academic Department of Radiation Oncology in the University of Leeds, U.K., and Dr. Hugh Pritchard from the Regional Cancer Centre at Clatters Bridge, Liverpool, U.K.

The expanded facility, which will house the London Regional Cancer Centre in 1988, will require an increase in space of some four- to five-fold over the present facility. This will be the first major increase in space for clinical and research activities in the London Centre in 20 years, over which period our patient load has tripled. These additional facilities will allow us to continue the search for excellence in all these areas of activity under new leadership -- as we watch the emergence of a new comprehensive cancer centre.

Haydn Bush, M.B.,B.S., Ph.D., F.R.C.P.
Director

NORTHEASTERN ONTARIO ONCOLOGY PROGRAM

LAURENTIAN HOSPITAL, SUDBURY

Director:

R.E.T. Corringham, M.B.,B.S.

Medical Oncologists:

T. Bozek, B.M.,B.Ch.
(Effective March 1987)
G.D. Goss, M.B.,B.Ch.
C.L. Sinnof, M.B.,B.Ch
(Effective April 1987)
M.D. Vincent, M.B.,Ch.B.
Effective February 1987)

Clinical Assistant:

G.M. Kane, M.B.,B.Ch.
(Effective January 1987)

Epidemiologist:

V. Nguyen, Ph.D.

Psychologist:

S. Steggles, M.A.

Administrator:

A. Pabani

Nurse Administrator:

C. McChesney, B.Sc.N.
(Effective April 1987)

Manager of Health Records:

R. Zambelli, C.C.H.R.A.(C)
(effective March 1, 1986)

1986 was a difficult year: the Northeastern Ontario Oncology Program (NEOOP or "Program") was constrained by lack of medical staff and space. In September we had to cut patient services by curtailing new patient referrals because the workload had exceeded the resources of the two medical staff.

However, in 1986, we laid the foundations for success in 1987. Three medical oncologists and a clinical assistant, who were recruited from overseas, are expected to arrive early in 1987. Agreement is near with local family practitioners to streamline palliative and primary care for cancer patients. The formation of a family-practitioner oncology group will enable our oncologists to function as tertiary care physicians and so enhance treatment and care. A department of clinical oncology has been established within Laurentian Hospital.

Preliminary discussions have been held with surgical specialists with a view to forming a tumor board. A joint program in pediatric oncology is being formulated with local pediatricians, the Hospital for Sick Children in Toronto, and the Pediatric Onthe Pediatric Oncology Group of Ontario.

Work started at the end of 1986 to expand temporary office space and this will be completed in March 1987. This will free up existing office space for clinical use in 1987. Mr. Anil Pabani became administrator and has been developing a business office, health records and computing. Ms Rita Zambelli is manager of health records. We are developing our own nursing program headed by Mrs. Terry Trottier, R.N., charge nurse and Mrs. Diane Blais, R.N., clinical teacher. With the oncologists and surgeons, they have developed a computerized drug delivery program (CADD) that will give "state-of-the-art" drug delivery for chemotherapy and pain control. In 1987 a nurse administrator will be hired.

As part of NEOOP's research base, Dr. Glenwood Goss is developing a clinical trials program. A part-time data manager and librarian have been hired to assist with this. The Sudbury-Manitoulin Tumor Registry has fulfilled its use as a benchmark for the Provincial Tumor Registry and will now become a specialized registry within the Provincial Registry. The Program has recruited Dr. Van Nguyen, an epidemiologist, to administer this registry; as a member of the OCTRF Division of Epidemiology and Statistics she will conduct epidemiological and demographic research in the North East. This research will develop a data base for planning for improved health-care delivery for cancer patients, cost projection and preventive programs. We continue to negotiate with the Faculty of Science, Laurentian University for laboratory space for research and we hope to establish a clinical scientist program in Sudbury in 1987.

The Program is also developing, for cancer patients, such support programs as psychosocial, dietary and pharmacy counselling. Mr. Shawn Steggles has been recruited to head the psychosocial program. NEOOP is also developing education programs. A successful two-day program was held in November with a nursing workshop, which was fully subscribed. A clinical day for physicians and health-care professionals drew an attendance of over 120 from across the region. Guest speakers came from the Hamilton Regional Cancer Centre and the Princess Margaret Hospital. In December the Program sponsored a successful palliative care workshop in the city as part of an initiative to promote better community palliative care services. Program physicians and staff have also participated in programs for the Northeastern Ontario Telehealth Network, which were received not only in the Province but across Canada.

R.E.T. Corringham, M.B.,B.S.
Director

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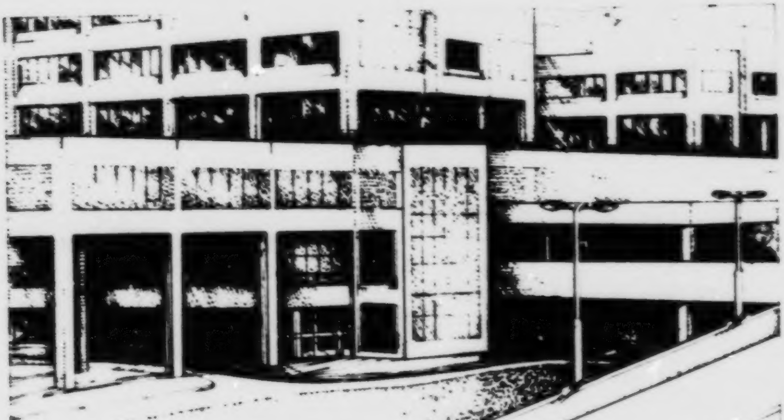
OTTAWA REGIONAL CANCER CENTRE

OTTAWA CIVIC HOSPITAL

AND OTTAWA GENERAL HOSPITAL



Director:

G.E. Catton, M.B.,B.S.

Radiation Oncologists:

C.J.E. Danjoux, M.D.
L. Eapen, M.D.
P. Genest, M.D.
A.L. Girard, M.D.
R.S.R. McDermot, M.D.
B.D. Nair, M.B.,B.S.

Medical Oncologists:

C. Cripps, M.D.
W.K. Evans, M.D.
J.A. Maroun, M.D.
D.J. Perrault, M.D.
D.J. Stewart, M.D.
S. Verma, M.D.
V.P.J. Young, M.D.

Clinical Assistants:

H. Bastianelli, M.D.
E. Brenken, M.D.
B. Goldsman, M.D.
K.R. Hopkinson, M.D.
I.A. Prosser, M.D.
K. Robillard, M.D.

Career Scientists:

H.C. Birnboim, M.D.
R.G. Liteplo, Ph.D.

Physicists:

J. Cygler, Ph.D.
L.H. Gerig, Ph.D.
P.M. Pfalzner, M.Sc.
G.P. Raaphorst, Ph.D.

Business Manager:

S. McAdam

Executive Secretary:

D. Pineau, C.M.S.

Nurse Administrator:

C.J. MacMillan, B.Sc.N.

Head Nurse (General Division)

L. Fawcett, R.N.

Senior Radiotherapy Technician:

R.P. Wallace, A.C.(T)

Managers of Health Records:

M.C. Therrien (Civic Hospital Division)
M.M. Brassard (General Hospital Division)

Lodge Supervisor:

J.M. Davidson, R.N.

Some staff changes took place in 1986. Drs. Ernst Brenken and Barry Goldsman joined the staff as clinical assistants in radiation oncology. Dr. Matthew Parliament, who was one of our Ivan Smith Scholars in 1982, began his training as a resident in radiation oncology. Drs. Joanna Cygler and Paul Johns joined the Department of Medical Physics. Three radiation technologist trainetrainees commenced their training – Cheri Gaddess, Janet Rintoul and Jim McLellan.

In the fall of 1986, Dr. Barbara Fisher passed the written and oral specialist examination in radiation oncology of the Royal College.

Bruce Faddegon, physicist-in-training, is now working on his Ph.D. degree in radiation physics with the National Research Council (NRC). He is under the supervision of our chief physicist, Dr. Peter Raaphorts, and Dr. Carl Ross of the NRC.

David Wilkins, who joined the Department of Medical Physics as a graduate student, is working on his Ph.D. degree in nuclear magnetic resonance. Under the supervision of Dr. Raaphorst, he will work on a research project with Dr. Ian Smith of the NRC.

Four radiation technology students passed the certification examination of the Canadian Association of Medical Radiation Technologists; on October 20, they received their certificates. Sharon Gay was one of the graduates and joined our fulltime staff.

The annual conference of the Ontario Association of Medical Radiation Technologists was held in Ottawa on April 30 to May 3, 1986. Dr. Wilbert Keon, Head of the Heart Institute of the University of Ottawa brought some of his transplant team and showed slides of their first artificial heart implant which they carried out the previous day.

In April, Dr. Jean-Claude Horiot of the Department of Radiotherapy at the Georges Francois Leclerc Centre in Dijon, France, visited our Centre. He gave two interesting presentations: one on interstitial curietherapy of tumors, and the other on hyperfractionation radiotherapy.

Also we had a visit from Dr. Patrick Hurteleopu, Co-ordinator of the Clinical Screening Group for the EORTC. He spoke on the clinical development of some new anthracyclines in Europe.

The 24th OCTRF Clinical Conference, "New Approaches to Cancer Management", was held in Ottawa on October 7. The 230 registrants included staff from all the regional cancer centres, Head Office, committee members, out-of-province delegates and pharmaceutical representatives.

The 14th International Cancer Congress in Budapest in August was attended by Drs. P. Raaphorst and L. Gerig (physicists) and Drs. W.K. Evans, D. Perrault and G.E. Catton.

The Selectron international meeting in Vancouver was attended by Drs. G.E. Catton, C.E. Danjoux and Mrs. F. Copeland.

The construction of the Lodge on top of the Ottawa General Hospital is underway and the Canadian Cancer Society launched a special fund raising campaign. Donations over $200 will be acknowledged on a plague in the lobby.

A sod-turning ceremony was held October 7 to mark the beginning of construction for the Maurice Grimes Lodge expansion. Twenty-two beds will be added to the 38 now in service.

The University of Ottawa training programs in medical oncology and radiation oncology received full accreditation from the Royal College.

With the assistance of Mead Johnson Canada, we hired a nutritionist for four months. She interviewed patients in the waiting room areas about their eating habits, gave advice to those with poor appetites or weight loss and prepared recipes using nutritional supplements for patients to sample.

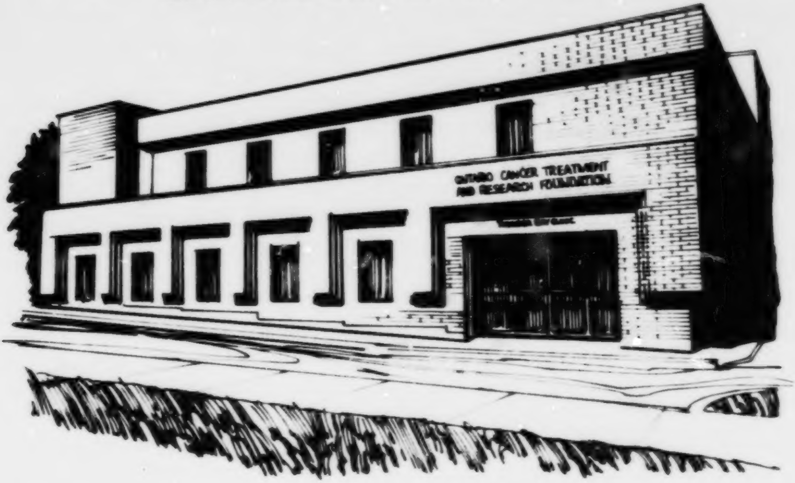
The Chinese government, in co-operation with the Ottawa Civic Hospital, sponsored three senior Chinese medical oncologists for one year's training at the Centre. In January, Drs. Xu, Zhang and Gu arrived. Under the supervision of Dr. W.K. Evans they will spent most of their time on the ward and in the outpatient department to gain clinical experience. They spent additional time in fields of their interest such as lymphoma pathology, chest radiology, and bone marrow transplantation.

In August, the Department of Experimental Oncology began a search for a third career scientist. The response to advertisements was good and a final selection should be made early in 1987. The theme of the department continues to be "molecular and cellular mechanisms of tumor promotion and progression". Research topics, supported by outside agencies, include: the involvement of oxyradicals in tumor promotion and progression; and perturbation of methionine metabolism, which may be important in tumor progression by disrupting normal patterns of DNA (methylcytosine). A new collaborative project has been initiated involving the study of an oncogene. The department's first graduate student, who is enrolled as a M.Sc. student in the Department of Microbiology and Immunology under the supervision of Dr. Birnboim, will participate in this study. The department played host to five outside speakers from Toronto, New York and Houston. This year, seven scientific papers were published or are in press.

G.E. Catton, M.B.,B.S., D.M.R.T., F.R.C.P.(C.)
Director

THUNDER BAY REGIONAL CANCER CENTRE

GENERAL HOSPITAL OF PORT ARTHUR


ONTARIO CANCER TREATMENT
AND RESEARCH FOUNDATION

Director:

J.F. Kotalik, M.D.

Radiation Oncologists:

S. Gulavita, M.B.,B.S.
M. McLean, M.B.,B.Ch.

Medical Oncologist:

S.D. Zaentz, M.D.

Clinical Assistant in Palliative Care:

J.A. Chalykoff, M.D.

Physicists:

M. Al-Ghazi, Ph.D.
P.D. Sharma, M.Sc.

Business Manager:

M.M. Ryan

Senior Nurse:

L. Bright, Reg.N.

Manager, Radiation Therapy:

J.V. Morgan, R.T.

Manager of Health Records:

V. Polischuk, C.C.H.R.A.(A)

Lodge Supervisor:

M. Magnusson

The year 1986 was a period of steady transformation for the Thunder Bay Centre. Our Siemens linear accelerator was unveiled formally in the presence of the Minister of Health of Ontario, Chairman, Executive Director and Secretary-Treasurer of the Foundation, and many other guests. The linear accelerator has been operating at 6MeV and 20MeV photon modes, and six different electron modes; at present about one-half of the patients requiring radiotherapy in our Centre are treated on this unit. We continue to train radiotherapy technologists in our Centre, and our latest graduate, Kasey Taylor, has joined the staff.

Our medical staff has remained stable except that Dr. Arlene McKnight resigned from her position of clinical assistant to enter private practice in family medicine. The Department of Medical Oncology has noted a considerable increase in the number of treatments. The number of patients entered into the clinical trials of NCIC, NCCTG and OCOG has increased to the point where our clinical trials secretary now bears an excessive load and we stand in urgent need of a clinical trials nurse. We are searching for such a person who will be supported from grants. The workload of our Department of Health Records seems to increase continually; the manager of this department, M.P. Winfield, has resigned and we welcome into this position Vicki Polischuk, who previously managed a similar department at the Lakehead Psychiatric Hospital. A new telephone system, which we installed in the fall, facilitates the work of all departments.

Throughout the summer, we were joined by two Ivan H. Smith summer students and also two physics students from Lakehead University, who came on the Harold E. Johns Studentships.

We have added three peripheral clinics – in Fort Frances, Geraldton and Dryden; these community services are much appreciated both by patients and medical staff in Dryden and area. Negotiations are underway concerning a peripheral clinic in Sioux Lookout to further improve our services to the vast area for which our Centre is responsible. Agreement has been reached with La Verendrye General Hospital at Fort Francis to establish a chemotherapy clinic there, which will be co-ordinated by Dr. Sanford Clare. As yet we have been unable to obtain any new funding for this program but at least training of nurses and physicians has been started for this chemotherapy outreach. Further improvements in this program are due in 1987.

In the area of research, work continues on the use of CT scanner for examination of tissue densities. We have ready for publication results of calibrations and further measurements on our new linear accelerator. Two psychosocial studies were completed in co-operation with Lakehead University: One examined the effects of intensive psychological support in a small group of selected patients, and the other examined the mastectomy visiting services in Northwestern Ontario. In the area of education, we continue to provide oncology rounds approximately once every two weeks. Our new patients conferences, held twice weekly, function as a tumor board and also as an educational experience. For one day last year, we assembled our staff for a review and planning session, which identified a number of areas for future development in the Centre and increased involvement of all staff members. As a result, a number of working groups were established around such issues as clinic overcrowding, co-operation between departments, scheduling, budgeting process, etc. These groups will report to the Centre's council which represents all employees.

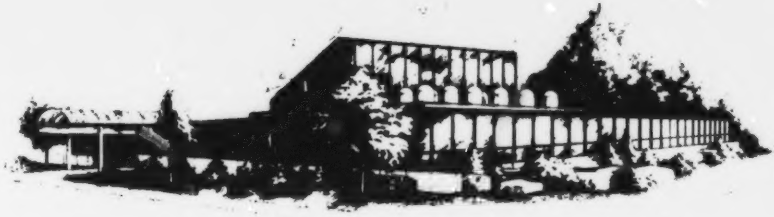
Reverends M. Steeves and E. Barg have evaluated the needs for pastoral care services in our Centre. They propose to establish a part-time position of a pastoral care worker in our Centre as a pilot project for two years and to fund this from private and community contributions. Planning for this position is underway.

Considerable attention was paid throughout last year to improvement in palliative care services. The physician in charge was given a permanent part-time position with our host hospital to assist in education and evaluation of activities. A Palliative Care Council was formed in the city with membership from executive directors of all acute care hospitals, the chronic care hospital, VON and Home Care, and representatives of the Canadian Cancer Society, the Council of Clergy and the District Health Council. This Council already appears to play a significant role in the co-ordination of such services and will be making further recommendations to the District Health Council. We have assisted in the birth of "Via Vitae Palliative Care Volunteers of Thunder Bay" – an organization to provide home visiting services and in this way supplement the work of available professionals.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

TORONTO-BAYVIEW REGIONAL CANCER CENTRE

SUNNYBROOK MEDICAL CENTRE



Director:

R.D.T. Jenkin, M.B.,B.S.

Radiation Oncologists:

I. Ackerman, M.D.
J.M. Balogh, M.D.
Ch.B. Catton, M.D.
P.A. Catton, M.D.
R.G. MacKenzie, M.D.
N.D. Mountifield, M.D.
C.S. Young, M.D.

Medical Oncologists:

R.A.A. Buckman, M.B.,B.Ch.
N. Iscoe, M.D.
I.J. Kerr, M.D.
J.J. Rusthoven, M.D.
D.J.A. Sutherland, M.D.

Clinical Assistants:

R.P. Hutchison, M.D.
H.M. Kocandrle, M.D.
J.A. MacKinnon, M.D.

Physicists:

R.B. Barnett, Ph.D.
H.B. Michaels, Ph.D.
P.F. O'Brien, M.Sc.
R.A. Siwek, Ph.D.

Administrator:

H.B. Wodinsky, M.H.Sc.

Administrative Assistant:

K.A. Nicholson

Business Manager:

G.B. Kolos, B.A.

Nurse Administrator:

C. Johnston, Reg.N.

Chief Radiotherapy Technologist:

S.V. Scott, A.C.(T), R.T.R.

Manager of Health Records:

M. Mistruzzi, C.C.H.R.A.(C)

1986 was a tumultous year at the Toronto-Bayview Regional Cancer Centre. On the one hand our annual growth of about 400 new patients a year continued. Thus we still handle the annual incremental growth for the whole of the Metropolitan region. As a consequence we now see over 3000 new patients annually compared with the planned upper limit of 2500 new patients for this "new" facility. An immediate corollary is that we no longer have appropriate space or equipment to meet the appropriate demands of our patient population. All our radiation treatment machines have to be operated 10 hours a day and, despite this, we have waiting lists for radiation treatment that have reached as long as six weeks and will lengthen during 1987. Finally, we no longer have the space to house the new staff needed to meet this increasing demand.

On the other hand strategic planning for oncology services in Metropolitan Toronto has been at fever pitch during the year. In the Spring the pressure to merge teaching hospitals into larger more effecient units brought a proposal that the Welleseley Hospital and the Princess Margaret Hospital move to Sunnybrook Medical Centre, the "Northern Campus" of the University of Toronto. This plan foresaw the creation of a giant cancer centre seeing 12,000 to 14,000 new patients annually, as a consequence of the integration of the Princess Margaret Hospital and the Toronto-Bayview Centre Regional Cancer Centre.

Late in the year, both the OCI and the OCTRF favoured a University Avenue location for a new Princess Margaret Hospital, in the middle 1990s, and an expansion of the Toronto-Bayview Centre to meet the continued Metropolitan Toronto growth in the interim. By the end of 1991 with the continued growth, our Centre will reach a size of 5000 new patients annually -- a maximum upper limit determined by the requirement for an appropriate balance in overall clinical activities within a large general teaching hospital. Thus by 1991, a third regional cancer centre will be needed for the Metropolitan Toronto region.

At the end of 1986, the appointment by the Minister of Health of a "factfinder" for oncology services within the Metropolitan Toronto region led to further detailed analyses of our long-term goals and requirements. Thus, in January 1987, preliminary plans will be prepared which will allow for the doubling of the size of the Toronto-Bayview Centre and for this doubling to be complete and functional by the end of 1989. The major implications of such a doubling for Sunnybrook Medical Centre include the need for a total of about 200 oncology beds. At the time of writing, we are awaiting the government's decision with regard to these major strategic moves.

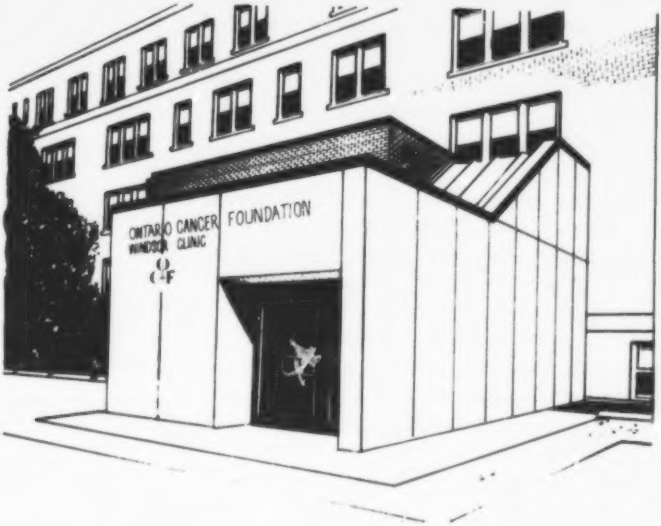
These exciting plans for the future have had thier short-term price. Our research space remains unfinished and the appointment of heads of the Divisions of Radiation and Medical Oncology have been delayed until our future size and shape become known.

Thus for the staff and patients of this Centre 1986 has been a time of short-term pain which we have borne in the hope of long-term gain.

R.D.T. Jenkin, M.B.,B.S., F.R.C.P.(C)
Director

WINDSOR REGIONAL CANCER CENTRE

METROPOLITAN GENERAL HOSPITAL



Director:

G.C.K. Mok, M.D.

Radiation Oncologists:

C.D. Springer, M.B.,B.S.

Medical Oncologists:

H.T. Abu-Zahra, M.B.,B.Ch.
D.B. McDonald, M.D.
S. Yoshida, M.D.

Clinical Assistants:

M. Foote, M.D.
P.X. Smith, M.D.

Physicist:

D. Smocovitis, M.Sc.

Business Manager:

E. Schwindt

Senior Radiotherapy Technician:

R. Macpherson Todd, R.T.

Senior Nurses:

A. Beaton, Reg.N.
M. O'Neill, Reg.N.

Manager of Health Records:

R. Van Der Borgh

The number of new patients registered at the Centre during 1986 was approximately the same as in 1985. The Centre had a busy year due to the shortage of radiation and medical oncologists. In June, Dr. Bruce McDonald, senior medical oncologist for the past 16 years, resigned to take up a new position as Director of Palliative Care Service in Providence Villa in Toronto. As a result we had to suspend temporarily our peripheral chemotherapy clinic program until a replacement became available. Dr. Z.Y. Alam, currently at the Ottawa Regional Cancer Centre, is expected to join the medical oncology staff on March 1, 1987. In the meantime, active negotiations are being conducted for a fourth medical oncologist. It is also expected that a new radiation oncologist will come on staff in early 1987. In May, Dr. Patrick X. Smith joined us as a clinical assistant in the medical oncology service.

In late October 1986, construction of a bunker for the dual-energy linear accelerator was near completion. The dual-energy Philips SL25 linear accelerator was delivered in November and around Christmas installation was nearly completed. Testing and calibrations by the manufacturer's technologists will begin in January 1987. We expect the equipment to be operational sometime in March. When the SL25 linear accelerator arrived, the old 280KV Picker deep x-ray machine was dismantled and, as requested by Dr. Peter Fitzpatrik, was donated to the Ontario Veterinary College for research purposes. A new Philips 100KV superficial x-ray was installed.

After a year's service, Elizabeth Gonzales, pharmacist, left the Windsor Centre to join the pharmacy staff at the Princess Margaret Hospital in Toronto. Mr. Thomas Chan, who worked in the pharmacy of the Metropolitan General Hospital and two other area hospitals, took over two weeks later.

The Department of Radiation Oncology participated actively in the OCOG clinical trials. On October 16, 1986, a symposium on the Management of Stage I Carcinoma of the Breast was held in Windsor with Drs. Robert Wilkinson, Roy Clark and Peter McCulloch as guest speakers. On September 17, 1986, Dr. Margaret Foote chaired a symposium on Pain Management with Dr. James Gowing of Kitchener as guest speaker.

The computer chart-tracking service, which was initiated in the Windsor Centre in 1986, has been working well. We look forward to the convenience of computer OHIP billing next year.

Working space is extremely limited at the Windsor Regional Cancer Centre. Office space is badly needed for additional medical specialists, nursing, physics as well as the clerical staff in the Medical Records Department. It is not possible to develop psychosocial services, breast, cervival and other screening clinics or any research programs due to this shortage of working space. Another expansion, or ideally the building of a new centre will have to be seriously considered in the near future, following the completion of the two larger centres in the Foundation.

G.C.K. Mok, M.D.
Director

SERVICE LOAD

The following tables describe the service load of the Foundation's seven regional cancer centres during the calendar year 1985.

In 1985, 45,397 patients were seen at the Foundation's regional cancer centres. Of these, 92% had malignant lesions and, of these lesions, 13,257 were new to the centres (Table I). Of cases referred for non-malignant conditions, 84% were first seen in 1985 (Table II). The majority of these, 1785, were seen in consultation. In all, 10,156 cancer cases were treated by radiotherapy (Table III); of these, 4643 were treated by cobalt units, 4190 by a linear accelerator, and 1323 by other methods of radiotherapy.

During the year, patients made 463,285 visits to the regional cancer centres and the majority, 451,796, were for treatment of malignant disease (Table IV). Of all radiation treatments, 85% were given on an outpatient basis (Table V).

As of January 1, 1982, with the implementation of the Patient Care Management System in the centres, it has been possible to retrieve data in more detail than was possible in previous years. However, the system has not been implemented completely and hence the tabulations are marked "provisional". It must be emphasized that these tables are comparable only with the service load tables published for 1982, 1983, and 1984; they are not comparable with those for the years before this.

TABLE I*

Malignant Caseload During 1985[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	1,124	174	435	46	1,406	3,185
Kingston	495	108	100	17	350	1,070
London	1,063	249	353	172	927	2,764
Ottawa	989	222	326	105	1,107	2,749
Thunder Bay	195	33	70	12	165	475
Toronto-Bayview	810	180	165	323	594	2,072
Windsor	330	74	253	7	278	942
TOTAL	5,006	1,040	1,702	682	4,827	13,257
	Cases Registered in any Previous Year					
Hamilton	382	216	817	25	4,542	5,982
Kingston	216	97	194	44	2,352	2,903
London	304	203	542	172	5,075	6,296
Ottawa	426	311	792	124	5,806	7,459
Thunder Bay	55	39	143	11	961	1,209
Toronto-Bayview	186	111	214	76	1,394	1,981
Windsor	96	70	438	15	2,173	2,792
TOTAL	1,665	1,047	3,140	467	22,303	28,622
TOTAL ALL MALIGNANT	6,671	2,087	4,842	1,149	27,130	41,879

* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE II*

Other (Non-Malignant) Caseload During 1985[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	25	—	16	14	235	290
Kingston	15	—	63	83	228	389
London	70	—	139	317	566	1,092
Ottawa	35	—	3	152	158	348
Thunder Bay	11	—	6	4	72	93
Toronto-Bayview	9	—	—	294	362	665
Windsor	3	—	20	—	164	187
TOTAL	168	—	247	864	1,785	3,064
	Cases Registered in any Previous Year					
Hamilton	—	1	—	—	26	27
Kingston	3	—	1	—	25	29
London	2	—	1	2	59	64
Ottawa	3	—	2	23	56	84
Thunder Bay	1	—	—	—	9	10
Toronto-Bayview	1	—	2	31	187	221
Windsor	2	—	1	—	16	19
TOTAL	12	1	7	56	378	454
TOTAL ALL OTHER	180	1	254	920	2,163	3,518

* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE III*

Cases Treated During 1985 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	195	205	151	40	17	42	—	650
Deep x-ray	97	17	—	—	1	—	167	282
Cobalt⁶⁰	1,144	409	586	1,127	296	637	444	4,643
Cesium¹³⁷	—	—	—	—	—	—	—	—
Betatron	—	—	2	—	—	1	—	3
Linear accelerator	595	465	1,278	1,050	1	801	—	4,190
Intracavitary	71	24	90	30	15	10	23	263
Interstitial	9	3	19	52	2	10	—	95
Moulds and applicators	—	1	8	—	1	—	—	10
Systemic isotopes	—	—	—	—	—	—	—	—
Others**	15	—	—	4	—	1	—	20
SUB-TOTAL	2,126	1,124	2,134	2,303	333	1,502	634	10,156
	Other Non-Malignant							
Superficial x-ray	3	5	32	—	9	—	—	49
Deep x-ray	1	—	—	—	1	—	3	5
Cobalt⁶⁰	19	12	13	21	2	7	2	76
Cesium¹³⁷	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	—	—	—	—
Linear accelerator	3	1	16	18	—	4	—	42
Intracavitary	—	—	—	1	—	—	—	1
Interstitial	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	11	—	—	—	—	11
Systemic isotopes	—	—	—	—	—	—	—	—
Others**	—	—	2	—	—	—	—	2
SUB-TOTAL	26	18	74	40	12	11	5	186
TOTAL[1]	2,152	1,142	2,208	2,343	345	1,513	639	10,342

* Provisional (transition period — see text)

**Others include radiation codes unknown

[1] A case can be treated by more than one method per year.

TABLE IV*

Service Load, 1985

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment			Non-Treatment		
	Radiation	Chemotherapy and/or Immunotherapy	Other	Simulation	Consultation or Follow-up	
	Visits for Malignant Neoplasms					
Hamilton	25,959	12,428	666	2,395	43,238	84,686
Kingston	14,320	2,620	513	1,597	18,842	37,892
London	34,279	7,545	1,063	2,248	41,609	86,744
Ottawa	33,970	10,444	1,474	2,845	57,817	106,550
Thunder Bay	5,967	1,883	407	351	8,350	16,958
Toronto-Bayview	18,872	3,524	1,006	1,826	33,813	59,041
Windsor	11,505	8,639	545	1,161	38,075	59,925
TOTAL	144,872	47,083	5,674	12,423	241,744	451,796
	Other Non-Malignant					
Hamilton	202	43	78	31	650	1,004
Kingston	143	74	287	25	822	1,351
London	493	214	610	22	2,139	3,478
Ottawa	466	17	424	46	858	1,811
Thunder Bay	78	13	33	3	290	417
Toronto-Bayview	136	3	452	12	1,660	2,263
Windsor	64	89	77	7	928	1,165
TOTAL	1,582	453	1,961	146	7,347	11,489
TOTAL ALL VISITS	146,454	47,536	7,635	12,569	249,091	463,285

*Provisional (transition period — see text)

TABLE V*

Treatments by Radiation During 1985, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Malignant Neoplasms															
Superficial x-ray	8	866	23	793	145	934	5	375	4	116	10	258	—	—	195	3,342
Deep x-ray	35	349	11	61	—	—	—	—	6	—	—	—	28	1,910	80	2,320
Cobalt^{60}	1,830	11,607	1,298	5,252	1,999	8,153	2,603	13,867	1,139	4,651	1,671	5,450	1,422	8,107	11,962	57,087
Cesium^{137}	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	—	15	—	—	—	—	—	9	—	—	—	24
Linear accelerator	862	10,288	946	5,893	4,398	18,510	1,791	15,197	—	15	1,832	9,670	—	—	9,829	59,573
Intracavitary	89	—	29	—	98	—	53	—	20	—	10	—	38	—	337	—
Interstitial	10	—	2	1	5	14	27	—	1	1	10	—	—	—	55	16
Moulds and applicators	—	—	1	—	—	8	—	—	—	1	—	—	—	—	1	9
Systemic isotopes	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Others**	8	7	—	—	—	—	—	21	—	—	—	5	—	—	8	33
SUB-TOTAL	2,842	23,117	2,310	12,000	6,645	27,634	4,479	29,460	1,170	4,784	3,533	15,392	1,488	10,017	22,467	122,404
	Other Non-Malignant															
Superficial x-ray	—	9	—	17	—	52	—	—	—	30	—	—	—	—	—	108
Deep x-ray	—	8	—	—	—	—	—	—	—	3	—	—	—	30	—	41
Cobalt^{60}	—	155	18	83	—	57	—	141	—	45	1	72	—	34	19	587
Cesium^{137}	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Linear accelerator	—	30	—	25	30	334	—	323	—	—	—	63	—	—	30	775
Intracavitary	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1	—
Interstitial	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	—	—	—	12	—	—	—	—	—	—	—	—	—	12
Systemic isotopes	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Others**	—	—	—	—	—	8	—	—	—	—	—	—	—	—	—	8
SUB-TOTAL	—	202	18	125	30	463	1	464	—	78	1	135	—	64	50	1,531
TOTAL OF ALL TREATMENTS	2,842	23,319	2,328	12,125	6,675	28,097	4,480	29,924	1,170	4,862	3,534	15,527	1,488	10,081	22,517	123,935

* Provisional (transition period — see text)
** Others include radiation codes unknown.

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Brantford — St. Joseph's Hospital
Burlington — Joseph Brant Memorial Hospital
Cambridge (Galt) — Cambridge Memorial Hospital
Guelph — Guelph General Hospital
Hamilton — McMaster Medical Centre and St. Joseph's Hospital
St. Catharines — Hotel Dieu Hospital
Welland — Welland County General Hospital

KINGSTON

Trenton — Trenton Memorial Hospital

LONDON

Chatham — Public General Hospital
Kitchener — Kitchener-Waterloo Hospital
London — Victoria Hospital, Westminster Campus
Owen Sound — General and Marine Hospital
Sarnia — St. Joseph's Hospital and Sarnia General Hospital
St. Thomas — St. Thomas-Elgin Hospital
Stratford — Stratford General Hospital
Wingham — Wingham and District Hospital
Woodstock — Woodstock General Hospital

OTTAWA

Cornwall — Cornwall General Hospital and Hotel Dieu Hospital
Pembroke — Pembroke Civic Hospital

THUNDER BAY

Fort Francis — Fort Frances Clinic
Geraldton — Geraldton District Hospital
Dryden — Dryden District General Hospital

TORONTO

North Bay — North Bay Civic Hospital
Owen Sound — General and Marine Hospital
Peterborough — St. Joseph's Hospital
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Sudbury — Laurentian Hospital
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F.A. Beale, M.B.,Ch.B.
H.A. Bean, M.D.
R.M. Clark, M.B.,B.S.
B.J. Cummings, M.B.,Ch.B.
A.J. Dembo, M.B.,B.Ch.
W. Duncan, M.B.,Ch.B.
P.J. Fitzpatrick, M.B.,B.S.
M.K. Gospodarowicz, M.D.
N.V. Hawkins, M.B.,B.S.
T.J. Keane, M.B.,B.Ch.
N.J. Laperriere, M.D.
B. O'Sullivan, M.B.,B.Ch.
D.G. Payne, M.D.
J.F. Pringle, M.B.,Ch.B.
G.A. Rawlings, M.D.
W.J. Simpson, M.D.
S.B. Sutcliffe, M.D.
G.M. Thomas, M.D.
P. Warde, M.B.,B.Ch.
J.L. Yeoh, M.D.

Diagnostic Radiology:

R. Blend, M.B.,B.S.
S. Herman, M.D.
J.R. Mayo, M.D.
P.Y. Poon, M.B.,B.S.
D.F. Rideout, M.B.,B.S.

Nuclear Medicine:

G.N. Ege, M.D.

Pathology:

J.S. Carruthers, M.D.
V.L. Fornasier, M.D.
G.J. Laroye, M.D.
B.J. Patterson, M.D.
M.E. Platts, M.D.
L.M. Sugar, M.D.
T. Treger, M.D.

Microbiology:

P.G. Tuffnell, M.D.

Physics (Clinical and Research):

H. Alasti-Hamed, M.Sc.
M.C. Archer, Ph.D.
M.J. Bronskill, Ph.D.
J.R. Cunningham, Ph.D.
A. Fenster, Ph.D.
S. Foster, Ph.D.
D.M. Galbraith, B.Sc.
J. Grant, M.Sc.
R.M. Henkelman, Ph.D.
R.P. Hill, Ph.D.
J.W. Hunt, Ph.D.
B. Japp, B.Sc.
J. Jezioranski, M.Sc.
P.M.K. Leung, Ph.D.
C. Mah, M.Sc.
A. Mosseri, M.Sc.
F.P. Ottensmeyer, Ph.D.
A.M. Rauth, Ph.D.
J.A. Rawlinson, M.Sc.
W.B. Taylor, B.Eng.
J. Van Dyk, M.Sc.
H.P. Webb, C.E.T.
G.F. Whitmore, Ph.D.
M. Yaffe, Ph.D.

Biological Research:

S. Benchimol, Ph.D.
R. Buick, Ph.D.
A.J. Cunningham, Ph.D.
J. Gariepy, Ph.D.
R.M. Gorczynski, Ph.D.
R. Gronostajski, Ph.D.
N. Iscoe, M.D.
V. Ling, Ph.D.
H. Llewellyn-Thomas, Ph.D.
T.W. Mak, Ph.D.
E.A. McCulloch, M.D.
R.G. Miller, Ph.D.
S. Minkin, Ph.D.
N. Miyamoto, Ph.D.
C. Paige, Ph.D.
J.E. Till, Ph.D.
D. Tritchler, Ph.D.

Biostatistics:

G. DeBoer, Ph.D.
D. Tritchler, Ph.D.

Administrator:

J.E. Ratz

Assistant Administrators:

E. Govoni
J.P. Holder, Reg.N.
T.J.D. West
W. Wilkinson

Manager of Health Records:

A. Buchanan, B.A., C.C.H.R.A.(C)

Librarian:

C. Morrison, B.A., M.L.S.

The struggle to continue the pursuit of excellence at the OCI/PMH has been difficult. Nevertheless, after more than a decade and one-half of effort by the staff in presenting the needs of the OCI/PMH, the message was heard and the door finally opened on a vision for the future.

The year was highlighted by the Ministry of Health's commitment of $200 million for provincial cancer services, including $133 million to rebuild the OCI/PMH. This has provided the catalyst needed to proceed with planning. The latter part of 1986 saw intensive effort by the OCI/PMH staff and Board, and other teaching hospitals to determine which site in Metro Toronto would provide the best overall environment for the Institute's patient care, research and teaching programs.

The joint Role Study conducted by the OCI/PMH and the OCTRF showed that the best model for the provincial cancer system is one with a large cancer hospital integrating patient care, research and education, plus a number of affiliated treatment centres attached to other hospitals in the region. The OCI/PMH believes 7000 new patients per year is the right size for the clinical component of the central hospital. Therefore the new OCI/PMH will be built to accommodate about 7000 new patients per year. As this report went to press, the OCI/PMH staff had expressed their preference for a downtown site on University Avenue. This site would provide the OCI/PMH with the unique opportunity to establish a world-class academic cancer centre with collaborative and interactive programs in a multi-hospital setting.

The Role Study also recommended a single provincial cancer agency with a Metropolitan Toronto Division. To facilitate this goal, the OCI/PMH and the OCTRF are working with a consultant to facilitate that merger.

When the Hon. Murray Elston, Minister of Health, announced the commitment of $200 million for provincial cancer services, he also stated that an additional $50 million would have to be raised through a public campaign conducted jointly by the OCTRF, the OCI/PMH, and the Canadian Cancer Society Ontario Division. The three organizations have retained a fundraising firm and are developing the plans for this joint campaign.

Another major accomplishment for the Institute this year was accreditation by the Canadian Council on Hospital Accreditation. The staff are to be commended for receiving a two-year award despite the tremendous space problems facing this organization. As part of the accreditation preparation, the corporate and medical by-laws were rewritten.

In the clinical divisions, service and clinical investigation have been maintained and further developed under increasingly difficult circumstances. The number of new patients served has remained unchanged from last year, although there has been a slight rise in the number of previously registered patients seen. This has led to a slight increase in the total number of patient visits even though the pediatric program was transfered to the Toronto-Bayview Regional Cancer Centre when Dr. M. Gribbin retired from practice. Drs. Bergeron and Majesky also left the staff of the PMH during the year. New appointments included Dr. F. Adams in neuropsychiatry, Dr. J. Mayo in diagnostic radiology, and Dr. P. Warde in radiation oncology.

Clinical studies aimed at improving management and/or understanding more about cancer continue actively in all site groups and with all modalities, even though resources are very tight. A large number of clinical studies in radiotherapy and chemotherapy alone or in some combination continue both as hospital-based studies or as part of regional/national investigations. Changes have to take place to accommodate new approaches such as the increased use of chemotherapy based on the outcome of studies at the PMH and elsewhere. When we have transferred much of our pheresis program to the Red Cross, we will be able to create more space for Day Care to accommodate this increase.

Work has continued on the northeast expansion. The upgraded magnetic resonance imager has been placed in its new space, and the first of two replacement cobalt units is being installed. This expansion will provide some additional limited space but will not resolve the major space problems facing this Institute over the next few years.

In the previous year, the Physics Division underwent its site review by the National Cancer Institute and was awarded a grant of $1 million annually for three years. In the fall of 1986 the Biological Research Division also underwent its site review and was again successful in attracting a high level of funding for the next three years.

The process of transition and renewal in biological research continued through 1986. Dr. Christopher Paige and Dr. Jean Gariepy have joined the staff since the last report, and Dr. Robert Phillips has moved to the Mount Sinai Research Institute.

The new site for the OCI/PMH will be announced in 1987 and we look forward to starting the planning for redevelopment.

R.S. Bush, M.D.
Director

TABLE I*

Number of Treatments Given in the PMH Department of Radiotherapy

April 1984 — March 1986

EXTERNAL BEAM	1985-1986	1984-1985
Superficial x-ray	1,415	1,856
Deep x-ray	2,764	3,136
Cobalt	44,149	41,210
Linear accelerators:		
Low energy	9,374	8,628
High energy	25,831**	23,612
Betatron†	1,933	4,921
TOTAL	85,466	83,363
Inpatient treatments	14,909	15,724
Outpatient treatments	70,557	67,639
TOTAL	85,466	83,363
SEALED SOURCES		
Intracavitary	243	251
Interstitial (needles, wires and seeds)	31	46
Strontium applicators	119	101
TOTAL	393	398

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1985-1986.

**Includes 5,066 treatments given at the Toronto-Bayview Regional Cancer Centre since July 1985.

† Betatron was removed from service July 1985.

TABLE II*

Services Provided by PMH at Peripheral Clinics

April 1985 — March 1986

CLINIC	NEW PATIENTS SEEN		PERIPHERAL CLINIC VISITS**	
	Malignant	Other	Malignant	Other
North Bay	143	7	1,393	57
Owen Sound	88	2	775	16
Peterborough	14	1	1,783	30
Sault Ste. Marie	43	4	732	14
Sudbury	15	1	1,076	10
Timmins	35	3	972	29
TOTAL†	338	18	6,731	156

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1985-1986.

**Including the visits when patients are first seen at peripheral clinics as well as subsequent visits for new and old patients.

†In addition, 51 patients were registered at the Sudbury Oncology Clinic, as distinct from the Sudbury Peripheral Clinic, and seen by Dr. R. Corringham. They had a total of 1,455 visits. Thirty-one of these patients are omitted from these tabulations because their records were not yet indexed.

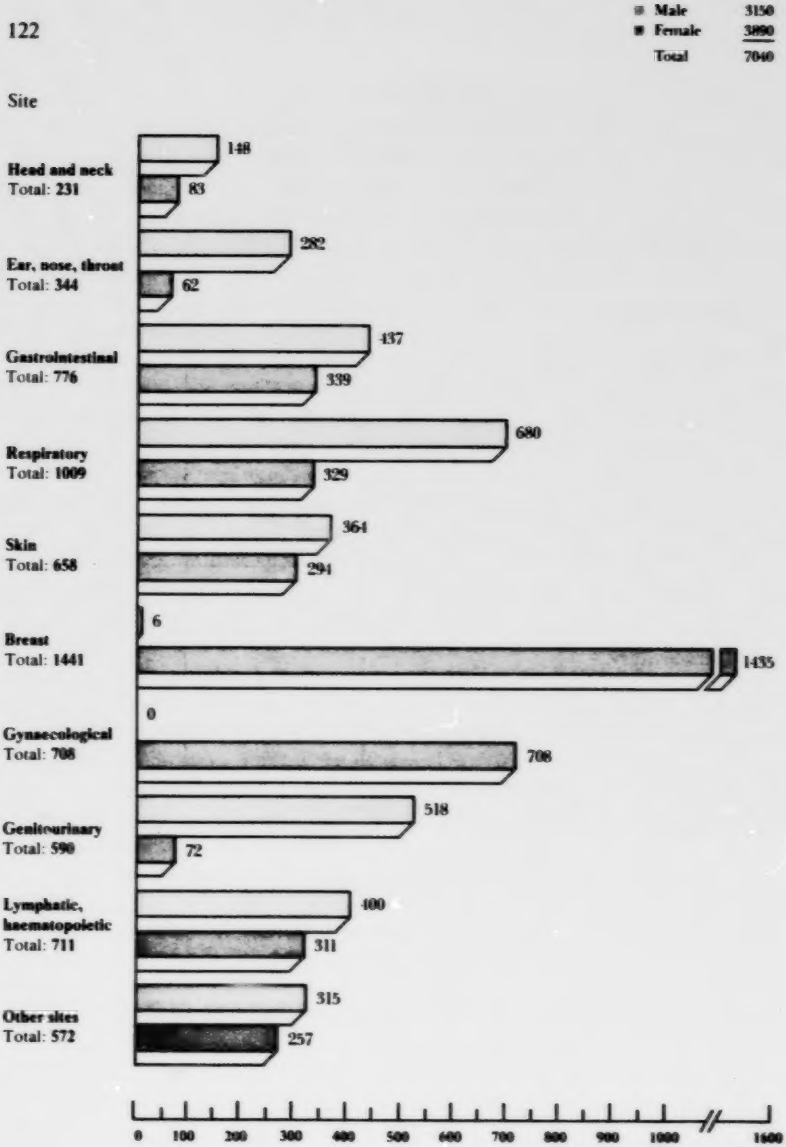

Fig. 1 **Cases of malignant disease at the Princess Margaret Hospital and distribution by site of malignancy and sex, April 1985 to March 1986.**
(Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1985-1986.)

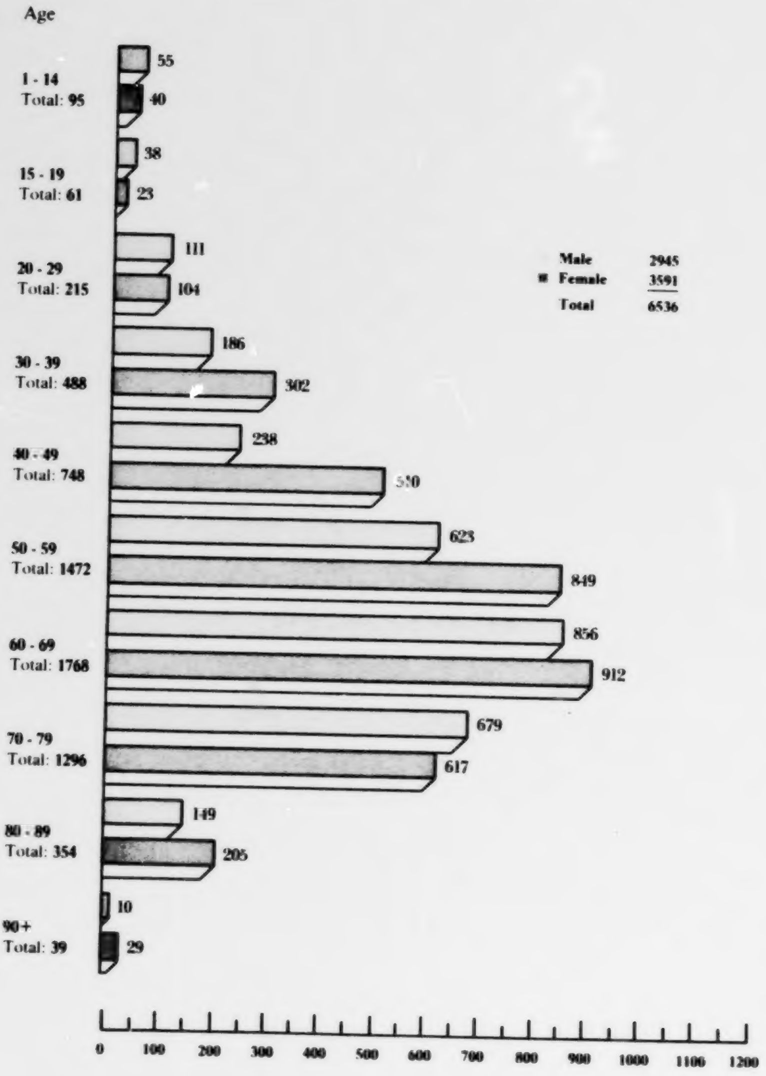

Fig. 2 **New patients with malignant disease seen at the Princess Margaret Hospital and distribution by age and sex, April 1985 to March 1986.**
(Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1985-1986.)

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources.

Drugs can be supplied only if attending doctors complete special prescription forms which are available from the Head Office, any of the Regional Cancer Centres, or the Princess Margaret Hospital. The completed form is mailed to the nearest Foundation centre or the Princess Margaret Hospital and the medication is mailed to the patient. The list of medications provided through the Federation is available on request.

The total cost of the drug service in 1985 was $662,563.20 – an increase of 16% from the $572,300.25 in the previous year (Table I). In 1985, 9,417 prescriptions were filled and the cost per prescription has increased to $70.36 from $62.86 in 1984.

TABLE I

Cost of Drug Service
1976-1985

Year	Payments for Drugs	Total Cost of Drug Service
1976	175,949.99	177,984.37
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20
1983	448,401.93	450,872.94
1984	569,966.52	572,300.25
1985	658,111.38	662,563.20

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for confirmed cases of cancer and the steroid-receptor assays for confirmed cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

During the fiscal period April 1, 1985 to March 31, 1986, 4,481 steroid-receptor assays and 46,128 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre
Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9
tel: (416)525-9140
ext. 6577

Kingston General Hospital
Dr. A.F. Clark
Stuart Street
Kingston, Ontario K7L 2V7
tel: (613)548-2121

Victoria Hospital
Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5
tel: (519)432-5241

Ottawa Civic Hospital
Dr. C. Lapkoff
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9
tel: (613)725-4431

General Hospital of Port Arthur
Dr. N. Escott
460 North Court Street
Thunder Bay, Ontario P7A 4X6
tel: (807)344-6621

Sunnybrook Medical Centre
Dr. A. Malkin
2075 Bayview Avenue
Toronto, Ontario M4N 3M5
tel: (416)480-4648

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre
Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416)521-2100
ext. 6577

Victoria Hospital
Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519)432-5241

Ottawa Civic Hospital
Dr. T. Ooi
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613)729-2511

Sunnybrook Medical Centre
Dr. D.J.A. Sutherland
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416)487-2722

University of Toronto
Dr. G.E. Mobbs
Medical Sciences Bldg., Rm. 7336
Toronto, Ontario M5S 1A8 tel: (416)978-3553

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1985, 6290 specimens were submitted by dentists (5420 in 1984).

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1985, 60,000 reports were submitted, a 12% increase over the 53,395 reports submitted in 1984.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation funds and administers six lodges for out-of-town ambulatory cancer patients attending the regional cancer centres for diagnosis and treatment. These lodges provide comfortable, supportive accommodation, with minimal supervision, at no cost to the patient. When beds are available, escorts are accommodated at minimal cost.

The Foundation provides this accommodation because the patient often has to travel a considerable distance to reach treatment centres. Without these facilities, the patient would be admitted to hospital at far greater expense to the Province.

The table below shows the current facilities, the number of beds and the patient days spent in each lodge during the fiscal year ended March 31, 1985.

		Number of Beds	Patient Days
HAMILTON	– Lakeview Lodge	20	588
KINGSTON	– Quinte-Thousand Islands Lodge	26	4,440
LONDON	– Thameswood Lodge	50	9,501
OTTAWA	– Maurice J. Grimes Lodge	36	7,731
THUNDER BAY	– Amethyst House Lodge	18	2,205
TORONTO	– Princess Margaret Hospital Lodge	105	22,849

Patients who require hostel accommodation while being treated at the Toronto-Bayview Regional Cancer Centre are housed in temporary facilities offered by Sunnybrook Medical Centre; 1,160 patient days were recorded in this fiscal year.

The Lakeview Lodge at Hamilton, which began receiving patients on November 18, 1985, had its official opening on April 22, 1986. As of September 1986, occupancy was running at approximately 80%. Lakeview Lodge can accommodate 20 patients in its 10 twin-bedded rooms. The structure contains shelled-in space, to be completed as necessary, for a further 18 patients.

In Ottawa, lodge facilities are being constructed at the Ottawa General Hospital. Also, the government has approved an expansion of the Maurice J. Grimes Lodge, located at Ottawa Civic Hospital.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation to any one of its regional cancer centres or to the Princess Margaret Hospital of those patients who live more than 25 miles from the centre and are considered to be in financial need. For patients 18 years or less, transportation is provided to the principal pediatric oncology treatment centres in the five health science complexes, namely:

HAMILTON — McMaster Medical Centre
KINGSTON — Kingston General and Hotel Dieu Hospitals
LONDON — War Memorial Children's Hospital, Victoria Hospital Corporation
OTTAWA — Children's Hospital of Eastern Ontario
TORONTO — Hospital for Sick Children

Usually transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1986, the total cost for transportation of patients was $799,209, compared to $658,205 for the fiscal year ended March 31, 1985.

CANCER INFORMATION SERVICE

The Cancer Information Service, funded by the Ontario Cancer Treatment and Research Foundation and the Canadian Cancer Society Ontario Division, is just completing its two-year pilot period. Funding to expand the project to a province-wide service has been approved by the Foundation and the Society. Plans are underway to expand the service in April 1987.

Since April 1985, when the toll-free telephone service began to provide the most up-to-date factual information on cancer and cancer-related resources to the general public, cancer patients and their families, health professionals, and the media, it has responded to over 6000 inquiries. The service is staffed by health professionals and trained volunteers who respond to calls using information of varying complexity.

The Service is continuing to provide access to the Physician Data Query (PDQ) computerized data base, developed by the National Cancer Institute and which is updated monthly, provides professionals with the most comprehensive information on cancer treatment for over 100 sites, including current research protocols.

The Service is well received; two user surveys have indicated that respondents were satisfied with the service they received. All respondents indicated that the information provided was useful, clear and concise; over 80% indicated that the information was new to them. All indicated they would use the Service again. Over 50% of respondents used the Service to find information they could not find elsewhere; another 45% wanted to confirm or clarify information from other sources.

Respondents mentioned some of the things they liked about the Service: the prompt response; the courteous and sympathetic counsellor; the patient explanations; the information given was well balanced and factual; no attempt was made to influence decision-making; confidentiality; and that printed material could be mailed to them for review. The only criticism was that the counsellor did not help the caller make decisions about his/her treatment or cure. Over 80% of respondents had taken action following their calls including: reading and sharing information; visiting their regular physician for evaluation of symptoms; attempting to reduce health hazards, e.g. smoking; or changing their diets.

In the first year of our province-wide service we expect to see an increase in our overall service, especially its use by professionals. Calls are answered Monday to Friday, between the hours 9:00 and 17:00.

RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

Two major changes occurred in 1986 relative to the administration of the Foundation's research program: Dr. J.C. Laidlaw joined the Foundation in September as Director of Research and Education, and a Research Advisory Panel was established replacing the long-established Research Committe and the more recently established Sub-Committee on Support of Research Personnel. We welcome Dr. Laidlaw and look forward to his guidance and assistance in our research endeavors.

As previously reported, the Ad Hoc Cancer Research Advisory Committee, which was established in 1985 to review cancer research throughout the Province, submitted its final report in July 1985. Subsequently the Board approved this report in December 1985. One of this Committee's major recommendations was that the Research Committee be replaced by a smaller group that would assume the responsibilities previously undertaken by both the Research Committee and the Sub-Committee. As a result, the Research Advisory Panel, with a membership of seven and three ex-officio members, met for the first time in June 1986. This group will meet bi-monthly to consider all issues relating to the Foundation's research programs and to consider the Ad Hoc Advisory Committee's recommendations. In light of current fiscal constraints, the Advisory Committee recommended that the Foundation's first priority be the continued support of career scientists working in the Regional Cancer Centres, and research associates/scholars working in the Health Sciences Centres and, if possible, the recruitment of additional personnel to the career scientist and research scholar programs. At present, the Panel is considering two additional recommendations, namely, (i) the establishment of a preventive oncology research program in Ontario, and (ii) a mechanism to provide financial support for clinicians/physicists working in the Regional Cancer Centres who wish to spend a significant amount of their time on research. It is recognized however, that unless the Ministry of Health provides additional funding, the Foundation cannot initiate either of these programs in the near future.

Career Scientists Program

This program was established to provide salary support, limited "start-up" funds for equipment and supplies and, if necessary, operating funds for up to two years for scientists working in the Regional Cancer Centres. The Foundation now supports 11 career scientists – 2 in Hamilton, 3 in Kingston, 4 in London, and 2 in Ottawa. Recently, Dr. Hugh Pross, career scientist at the Kingston Centre, assumed the position of Head of the Department of Microbiology and Immunology at Queen's University; as a result, negotiations are underway to appoint a replacement for him in the near future. In addition, we have received approval to recruit one additional scientist at the Hamilton Centre and one at the Ottawa Centre. Eventually the Foundation hopes to support 20 career scientists (4 in each university-affiliated centre, namely, Hamilton, Kingston, London, Ottawa, and Toronto-Bayview). Generally these appointments are considered "life appointments" but are dependent upon the maintenance of peer-reviewed grant support, publications in peer-reviewed journals and periodic reviews.

Research Associates and Research Scholars

For many years, the Foundation has supported a number of scientists working in the Health Sciences Centres on a full- or part-time basis (research associates). These appointments were similar to the career scientist appointments and continued support is dependent upon the same criteria as career scientists. In 1986, Drs. S.K. Liao and K.M. Stavraky terminated their associateships hence the Foundation now supports five research associates -- all in the Toronto area.

In an effort to recruit young investigators into cancer research, the Foundation has phased-out the research associates program a few years ago, with the understanding that the support of all associates currently supported would continue in accordance with their terms of the original appointments. This program has been replaced by the research scholar program, which provides support for a five-year term, once renewable, with similar criteria to that of career scientists. Reviews are held at the end of the fourth year for reappointment for a second term. To date, three research scholars have been appointmed, but Dr. John Powe (Victoria Hospital, London) terminated his appointment to return to the USA. Dependent upon available funding, a third competition may be held in the Fall of 1987 for the appointment of research scholar(s). In addition to providing salary support, the Foundation provides limited funding on a "one-time" basis for supplies and/or equipment.

Senior Scientific Staff at the Ontario Cancer Institute

In addition to providing support for career scientists, research associates and scholars, the Foundation provides salary support and "core" funding for supplies, utilities, etc., for the senior scientific staff in the Division of Biology and Physics at the Ontario Cancer Institute. The Annual Research Report published by the Ontario Cancer Institute incorporating the Princess Margaret Hospital gives information relating to the projects being carried out by this group.

Research Unit of the OCTRF

The Foundation also supports members of the Foundation's Division of Epidemiology and Statistics in their research projects. Members of the Unit, which has been affiliated with the Department of Preventive Medicine and Biostatistics at the University of Toronto since 1978, compete for operating funds through the various external granting agencies. In addition to their individual research pursuits, they assist research workers throughout the Province by providing epidemiological and biostatistical information, respond to requests from the Ministry of Health on relevant issues, and provide information to the scientific community and general public.

Grants-In-Aid Program

As previously reported, this program was phased-out several years ago because of the serious financial constraints facing the Foundation. Progress and final reports on projects supported through this program have been included in successive issues of *Cancer in Ontario*. The last of these reports appear in this issue. Future issues will contain reports of projects undertaken by the career scientists, research associates, research scholars, the Research Unit and, perhaps to a limited extent, reports on projects undertaken by members of the Ontario Cancer Institute.

OCTRF Core Grants

In addition to providing salary support, limited "start-up" funds and operating funds, where necessary, the Foundation provides an annual award to each Regional Cancer Centre with a research unit to cover the uncommon needs of the career scientists. These funds cover such items as secretarial support, travel costs for investigator(s) or for guest speakers, service contracts, etc. These costs generally are not provided through external operating grants.

Janet Downs
Research Secretary

The Ontario Clinical Oncology Group

In the spring of 1984, the group initiated two large Phase III trials to compare methods of treatment in the two most common stages of female breast cancer. The Stage I trial (small primary tumor in the breast and pathologically negative axillary nodes) compares conservative surgery (lumpectomy) alone with lumpectomy followed by adjuvant radiotherapy to the affected breast. By October 30, 1986, 415 patients had been entered in this trial from the participating OCTRF Regional Cancer Centres – Hamilton, London, Ottawa, Thunder Bay, and Windsor – and the Princess Margaret Hospital in Toronto. The Stage II breast cancer trial (primary tumor removed from the breast, and some axillary nodes pathologically positive for metastatic disease but with no evidence of systemic cancer) compares a three-month intensive adjuvant chemohormonal therapy with a nine-month, less-intensive adjuvant therapy in the postoperative period. By October 30, 1986, 375 patients had been entered from the participating OCTRF Regional Cancer Centres in Hamilton, London, Thunder Bay, and Windsor.

The total planned intake for each of these trials is 800 patients. Accrual is excellent and should be completed on target. The principal investigators and members of the data centre (at McMaster University) continue to travel to each local centre for conferences with participants and educational sessions with local medical groups.

At our Clinical Investigators Workshop in April 1985, one of the tutorial groups examined a proposal to reverse sputum metaplasia in chronic cigarette smokers with a Vitamin A derivative. This innovative idea has been developed into a placebo controlled study of etretinate in long-term cigarette smokers. Recruitment of volunteers began in August 1986 and approximately 110 subjects will be studied prospectively.

Co-investigators from London and Toronto have devised a therapeutic study in endometrial carcinoma: A four-arm comparison of standard versus wide-field radiotherapy and medroxyprogesterone versus placebo. Most Ontario centres have expressed interest in this study and it has been submitted for external funding.

The second annual three-day workshop on clinical investigation was held in mid-April 1986 at McMaster University in the Department of Clinical Epidemiology and Biostatistics. The 20 participants came from the OCTRF Regional Cancer Centres, the Ontario Cancer Institute and the University of Toronto. Twelve faculty members from McMaster University acted as plenary session lecturers and tutors for the three tutorial groups. At the end of the workshop, each of the groups presented proposals for a preliminary clinical trial which they had developed during the sessions. The following topics were identified and discussed during the workshop: the research question; design and architecture; selecting a sample and defining a manoeuvre; outcome and measurement; sample size and statistical analysis; and ethical considerations. The participants found this an excellent educational experience.

P.B. McCulloch, M.D., F.R.C.P.(C)
Program Co-ordinator

OCTRF RESEARCH ASSOCIATES IN THE HEALTH SCIENCES CENTRES

Toronto Western Hospital

Michael A. Baker, M.D.
Herbert F. Haberman, M.D.

University of Toronto

John G. Connolly, M.D.,	Department of Surgery
Brenda L. Gallie, M.D.,	Department of Ophthalmology
G. Elizabeth Mobbs, Ph.D.,	Department of Surgery

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Hamilton Regional Cancer Centre

IN VITRO BIOLOGICAL STUDIES OF PHOTODYNAMIC THERAPY USING A MULTICELL SPHEROID MODEL*

W.P. JEEVES**, *Hamilton, Ontario*

Photodynamic therapy (PDT) holds considerable promise as a new modality for the palliation or cure of patients with localized solid tumors[1,2]. During PDT, the tumor is irradiated with high-intensity visible light after intravenous administration of the photosensitizing drug, hematoporphyrin derivative (HPD). However, to date the application of PDT has been largely empirical and, as yet, we know relatively little concerning the extent to which tumor response to PDT is modified by changing treatment variables, or by variations in oxygen and nutrient concentration within solid tumors.

We are using multicell spheroid cultures of the V79 Chinese hamster cell line to study the role of several treatment and microenvironmental parameters in modifying the response of tumors to PDT. The kinetics of the uptake and distribution of HPD into spheroids of different sizes have been examined by fluorimetry and fluorescence flow cytometry. Variations in the response of these spheroids to HPD and red light, as assessed by the end point of growth delay, are being correlated with changes in a variety of experimental conditions, e.g. HPD concentration, light intensity, spheroid size, and O_2 concentration, to separate the relative contributions of these factors to spheroid-cell killing by PDT.

To date our results suggest that the uptake of HPD into spheroids may be diffusion-limited[3], and we are testing the possibility that a gradient of HPD may exist throughout the spheroid volume. We have found that, while neither HPD nor red light alone appear to affect significantly the growth characteristics of spheroids, moderate drug and light doses in combination can achieve substantial growth delay. Following treatment with HPD and red light, the kinetics of spheroid volume change and cell loss, and the potential for regrowth, depend on both the drug and light exposure levels. Differences in the forms of growth delay curves, obtained under different conditions, suggest that different mechanisms may operate to delay and ultimately prevent regrowth of PDT-treated spheroids. Furthermore, we have found that the growth delay response is oxygen-dependent, and HPD-treated spheroids that are exposed to light in the absence of O_2 exhibit no significant growth delay.

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*CS-105.

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton.

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CISPLATIN-INDUCED NEPHROTOXICITY*

G. SINGH**, *Hamilton, Ontario*

Cisplatin, a relatively new chemotherapeutic agent, has been applied to the treatment of several human malignancies. However, its usefulness is limited because during prolonged use it produces significant impairment in renal function. A mouse model was used to elucidate the cellular mechanism of cisplatin-induced nephrotoxicity. Single and multiple doses of cisplatin and transplatin were injected intraperitoneally to C57BL/6J mice and their serum urea nitrogen was measured every 24 hours for six days to detect early kidney dysfunction. Also electronmicrographs were made of cisplatin-treated mouse kidney.

Our data show that a high dose of cisplatin or multiple low doses induced nephrotoxicity as in the mouse-model. Predominantly, the anatomical lesions so induced were located in the S-3 segment of the proximal tubule. The electronmicrographs demonstrated that the lesions were at the mitochondrial level and morphometric analysis demonstrated a significant reduction[1] in the number of mitochondria in cisplatin-treated mouse kidney. These changes were not observed in either transplatin or carboplatin-treated mice. Further in vitro data showed that Rhodamine-123 fluorescence disappears in cisplatin-treated HF172 cell mitochondria.

Currently we are attempting to determine whether mitochondrial damage induced by cisplatin is caused by mTDNA damage or by lesions of the mitochondrial membrane. Preliminary data from southern-blot analysis show that cisplatin causes extensive mitochondrial DNA damage in vitro. Further in vitro studies are in progress and restriction mapping is being done to localize any hot-spots on mTDNA for cisplatin.

In conclusion, these studies provide a novel toxicological approach to delineate cisplatin-induced nephrotoxicity. They also support the hypothesis that mTDNA may be a critical target of cytotoxic drugs especially some used in the treatment of cancer.

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*CS-106-1.

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton.

ADDITIONAL INVESTIGATIONS

Dr. W.M. Hryniuk, Director of the Hamilton Regional Cancer Centre, reports on the following clinical research investigations:

ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

In co-operation with the London, Thunder Bay, and Windsor Regional Cancer Centres, we are conducting a randomized controlled trial to determine the efficacy of a short, intensive 12-week course of chemohormonal therapy compared with a standard 36-week course of chemotherapy. Benefit will be assessed with respect to reduction in recurrence rate and mortality, while toxicity will be assessed in terms of side effects, associated morbidity, and reduced quality of life. If treatment shows a similar failure rate, the expected decreased toxicity would make a 12-week course preferable in Stage II breast carcinoma. On the other hand, if the shorter treatment is associated with an increase in relapse rate and/or mortality this would help clinicians determine the optimal duration of adjuvant chemotherapy. To date, 350 women with Stage II disease have been randomized. This trial is supported by the Ontario Clinical Oncology Group and funded by the Medical Research Council of Canada.

QUALITY OF LIFE IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

We have developed a new comprehensive index -- the Breast Cancer Chemotherapy Questionnaire -- to measure toxicity and quality of life in women receiving adjuvant chemotherapy for breast cancer. Preliminary analysis suggests that this index is valid, reliable, and responsive to change. We have used this clinical trial to explore the relationship between utility -- a measure of the worth of the health state -- reported directly by the patient, and quality of life, as estimated indirectly by the quality of life questionnaires. A modified time trade-off technique allows patients to estimate how many years in their present state of health they would trade for a shorter life span in good health. The time trade-off method gives an estimate of the "utility" of life while the patient is receiving chemotherapy. Utility may prove to be a useful measure of quality of life.

VENOUS THROMBOEMBOLIC DISEASE IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

Although thrombosis has been reported in a variety of solid tumors, these reports are only descriptive -- case series or case reports. No good case control or cohort studies have been done to determine the association (relative risk) between cancer and thrombosis. The postulated mechanisms for venous thrombosis in cancer patients are: (1) malignant cells induce clotting; (2) drugs used in the treatment of cancer produce thrombosis; and (3) associated conditions such as bed rest, surgery, and sepsis predispose to thrombosis. We are conducting a cohort analysis in which all those receiving adjuvant chemotherapy for Stage II breast carcinoma undergo impedance plethysmography and Doppler ultrasound to determine the true rates of thrombosis in such patients.

STAGE I BREAST CANCER

We are active participants in the OCOG Stage I breast cancer trial evaluating the role of local breast irradiation in women who have had "lumpectomies".

PILOT STUDIES IN STAGE IV BREAST CANCER

A Phase II study is being conducted in women with Stage IV breast cancer to measure the dose intensity of mitoxantrone. Similarly a Phase II study is being conducted to evaluate a "super" fluorouracil, Adriamycin, and cyclophosphamide regimen in advanced breast cancer.

CO-OPERATIVE GROUP TRIALS

We are following selected protocols of the NCIC and OCOG for myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, non-small-cell carcinoma of the lung, small-cell carcinoma of the lung, ovarian carcinoma, and Stage I breast cancer.

CHEMOTHERAPY STUDIES IN HEAD AND NECK CANCER

A randomized controlled trial is being done to determine the optimum sequence for the administration of methotrexate and 5-fluorouracil in head and neck cancer. This trial will test a biochemical model which describes the interaction of the two drugs. The present sequence is a comparison of the standard therapy of simultaneous administration with an 18-hour delay. The trial is funded through NCIC, and to date 101 patients have been accrued.

In a separate study, patients with recurrent head and neck cancer, and those presenting with newly diagnosed disease but ineligible for the methotrexate/5-fluorouracil sequence study, are treated with standard-dose methotrexate and randomized to leucovorin rescue, or an identical placebo in a double-blind design. The aim is to determine the influence of leucovorin on the antitumor effect of standard-dose methotrexate and, at the same time, to determine the magnitude of protection it achieves from standard-dose methotrexate toxicity. Thus far, 42 patients have been accrued to the study, which is funded through Cyanamid Canada Inc.

SMALL-CELL LUNG CANCER

A pilot study has been completed evaluating the efficacy of tamoxifen and verapimel added to standard chemotherapy for small-cell lung cancer. Experimental evidence suggests that these agents can decrease resistance to anticancer drugs.

We are now evaluating the role of these modifiers in a randomized trial in patients with extensive small-cell lung cancer.

STUDIES IN ACUTE MYELOBLASTIC LEUKEMIA

The Hamilton Centre is a founding member of the Leukemia Intergroup, funded through the National Institutes of Health, Bethesda, Maryland. This co-operative group of seven centres is seeking laboratory and clinical predictors of treatment outcome in acute leukemia. All patients are treated on uniform protocols and laboratory studies are done on bone marrow and peripheral blood cells. Pharmacologic endpoints are also being measured. Current studies of high priority are: The influence of chemotherapy on oncogene expression of freshly isolated leukemia cells; and in vivo cell kinetics of leukemic cells using infusions of bromodeoxyuusing infusions of bromodeoxyuridine. Bromodeoxyuridine-labelled cells are then identified in vitro using a monoclonal antibody to this compound.

STUDIES IN CANCER METASTASES

Dr. William Orr is studying factors that influence tumor-cell chemotaxis and the growth of metastases at different sites. The studies are funded by NCIC. His major interest is in variables that influence metastases of cancer cells to lung and bone; he is placing special emphasis on the role of the inflammatory response in tumor-cell metastases and the role of bone resorption at both metastatic sites.

STUDIES ON ACTION MECHANISM OF ANTITUMOR DRUGS

Dr. Gurmit Singh is investigating mitochondria as a target for chemotherapeutic agents. The model is the influence of cis-platinum on nephrotoxicity and on antitumor effects. He has developed a murine model for nephrotoxicity from cis-platinum and also has developed a method for identifying mitochondrial DNA as distinct from nuclear DNA within cells. With these methods, he hopes to distinguish between primary and secondary mitochondrial damage due to chemotherapeutic agents. The study is funded by the Medical Research Council of Canada.

Kingston Regional Cancer Centre

PHOTOCHEMOTHERAPY: CHEMICAL AND BIOLOGICAL CORRELATIONS*

J.C. KENNEDY** and R.H. POTTIER†, *Kingston, Ontario*

Our objectives are: (a) to identify the relationship between certain chemical, photochemical, and/or photophysical characteristics of a selected group of photosensitizing agents, and their tumor-localizing, tumor-photosensitizing, and/or neurotoxic properties; and (b) to use the above information as a basis for the rational selection or synthesis of improved photochemotherapeutic agents. Since no single centre has the necessary equipment and expertise to carry out such a broad program, three centres are collaborating: Paisley College, Scotland; Royal Military College, Kingston; and Queen's University, Kingston. The Paisley College group is obtaining measurements of triplet state lifetimes and extinction coefficients, the efficiency of triplet state formation, the rates of reaction of triple state sensitizers with various molecules of biological importance, the resulting yield of singlet oxygen, and the characteristics of the radical ions that are formed. This is a preliminary screen to identify photosensitizing compounds that have useful characteristics. The Royal Military College group is measuring absorbance spectra, fluorescence emission spectra, fluorescence excitation spectra, and several different types of partition coefficients under various environmental conditions. Iso-electric points are being measured also, and where solubility limits permit, the pK's of the various ionic species are being obtained by volumetric titration. It is possible in this way to identify the ionic species that are likely to be present in the interstitial fluid of both normal and malignant tissues, and also to identify conditions and factors that might influence the state of aggregation of certain photosensitizers in vivo. The Queen's University group is measuring systemic toxicity, neurotoxicity, phototoxicity, tissue distributions and half-lives, and therapeutic effectiveness of those sensitizers that survive the photophysical and photochemical screening process.

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*CS-101-1.

**Career Scientist, OCTRF Kingston Regional Cancer Centre; and Associate Professor of Oncology and of Pathology, Queen's University, Kingston.

†Professor of Chemistry and of Chemical Engineering, Royal Military College, Kingston; and Associate Professor of Urology, Queen's University.

Various porphyrins, phthalocyanines, chlorins, and hybrids of such compounds are now in the process of characterization and evaluation. In addition, we are studying the tissue specificity of the photoprotection provided by the radioprotective agent WR-2721, and are evaluating ALA-induced protoporphyrin biosynthesis as a possible technique for producing tissue-specific photosensitization and fluorescence.

This project is supported by a grant from the Medical Research Council of Canada.

STUDIES ON HUMAN CYTOTOXIC EFFECTOR CELLS*

H.F. PROSS**, *Kingston, Ontario*

The primary focus of our basic and clinical research has been the study of human cytotoxic (antitumor) lymphocytes. This report describes the results of clinical studies on natural killer (NK) cells, especially with respect to the association between NK-cell activity and malignant disease. NK cells exist in the blood of all normal donors, from birth to old age. Over the past 12 years we have assessed the NK (K562) activity of monocyte-depleted peripheral blood lymphocytes in 535 normal donors and 1600 patients with solid tumors. Data were expressed as activity relative to normal controls (RNK). Chart abstraction and computer data entry are complete for 307 patients -- 1455 assays. Patients were tested from 1-34 times (median, 3) and the mean cytotoxicity was calculated for each patient within each disease status: "no evidence of disease" (NED); "local recurrence and/or local nodal disease"; "metastatic disease in one site" (limited metastases); and "metastatic disease in 2 or more sites" (advanced metastases). As previously reported, the RNK of patients with NED or local disease did not differ from normal, but was significantly reduced in patients with metastatic disease. We assessed the relationship between NK activity and survival using the proportional hazards test, and plotted survival curves (from diagnosis) for each quartile of relative NK activity for each group. Although the results suggested a relationship for the data set as a whole ($p<0.09$), no significant relationship was found within the subgroups. These data indicate either that NK activity is of no prognostic significance with respect to survival, or that larger subgroups are needed to show statistically significant differences. Then further analysis was done on the data from patients who had developed metastatic disease. These data were handled much like the survival data except that all patients analyzed had reached the endpoint (i.e. metastatic disease) and were being studied with reference to "metastasis-free" survival time from diagnosis. This subgroup of 91 patients showed a statistically significant ($p<0.029$) correlation between high NK activity and prolonged metastasis-free survival time. This finding is compatible with data showing that animals with high NK activity are more resistant to metastases than those with low NK function. Because it is possible that some of these patients, who are now well, will go on to develop metastases, we will analyze the clinical data again later to determine whether the observed differences persist in a larger patient group.

This study was funded by the NCIC, MRCC, and OCTRF.

**Former Career Scientist, OCTRF Kingston Regional Cancer Centre; Professor of Oncology, and Head of Department of Microbiology and Immunology, Queen's University, Kingston.

DRUG RESISTANCE IN HUMAN LUNG TUMORS*

S.P.C. COLE**, *Kingston, Ontario*

A major obstacle in clinical oncology is the development of resistance to antineoplastic agents. To study this problem in small-cell lung cancer (SCLC), we have isolated a multidrug resistant (MDR) variant of the SCLC cell line, NCI-H69. This cell line, designated H69AR, was obtained by selection in gradually increasing doses of Adriamycin. In contrast to many previously described MDR cell lines, H69AR exhibits no detectable evidence of enhanced expression of P-lycoprotein at the RNA, DNA or protein level. To gain some insight into the membrane biomolecules associated with MDR in our system, we have raised a panel of murine monoclonal antibodies (MAbs) specific for H69AR cells. The cell surface specificity of these MAbs has been ascertained by cell ELISA, indirect immunofluorescence and fluorescence-activated cell sorter analysis. None of the MAbs cross react with the well-known MDR Chinese hamster ovary cell line, CHO*R*C5, although three MAbs show some cross reactivity with the MDR human ovarian cell line, A2780 AD645. Fixation of H69AR cells in methanol or formalin adversely affects the reactivity of some MAbs but not others. Further functional and biochemical characterization of these MAbs and their antigens will determine whether these MAbs may be useful in the study of MDR in SCLC.

This project is funded by the Medical Research Council of Canada.

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*CS-107-1.

**Career Scientist, OCTRF Kingston Regional Cancer Centre; and Assistant Professor of Oncology, and of Microbiology and Immunology, Queen's University, Kingston.

London Regional Cancer Centre

EFFECT OF ANTHRACYCLINES ON MULTICELL SPHEROIDS AND THE USE OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (MRS) TO MONITOR CARDIAC DAMAGE CAUSED BY ADRIAMYCIN*

W.R. INCH**, *London, Ontario*

Two projects are in progress; the first is a study of the effects of Adriamycin, mitoxantrone and menogaril on the V79 multicell spheroid; the second is an investigation of cardiac damage caused by Adriamycin using ^{31}P spectra obtained from a small bore (30 cm diameter) super-conducting system MRS.

Assessment of Damage by Anthracyclines

The multicell spheroid, an in vitro model of a tumor nodule, consists of a fraction of well-oxygenated, dividing cells in close proximity to the surrounding medium, and a fraction of hypoxic, nutritionally deprived cells at a distance from the periphery.

We have studied the cytotoxic effect of Adriamycin, mitoxantrone, and menogaril on V79 Chinese hamster lung fibroblasts growing as exponential monolayers and as multicell spheroids. In addition to whole spheroid survival, we have serially dissociated the spheroids, after a two-hour, drug-medium incubation into two equal cell fractions representing the outer oxygenated and inner hypoxic subpopulation of cells. The two subpopulations were plated separately and assayed for clonogenic survival.

Multicell spheroids, incubated with Adriamycin, mitoxantrone or menogaril for two hours, are 6 to 300 times more resistant (based on LD_{90} or area under the curve at 10% survival) than exponentially growing monolayers (Table I). This resistance is not due solely to the hypoxic fraction at the interior of the spheroid because the outer layer also exhibits a 2 to 60 increase in fold, compared to monolayers. The reduced cell kill in the tumor model may be due to the diffusion, and uptake kinetics, of the three anthracyclines by the spheroids.

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*CS-100-1.

**Career Scientist, OCTRF London Regional Cancer Centre; and Professor of Radiation Oncology and of Biophysics, University of Western Ontario, London.

We are measuring uptake of the three anthracyclines by monolayers, outer spheroid cells, and inner spheroid cells to determine whether the variable sensitivity observed is due to metabolic activity, or a difference in drug accumulation.

TABLE I

Survival of Monolayers and Spheroids Exposed to Adriamycin, Mitoxantrone or Menogaril

	MONOLAYERS (M)	SPHEROIDS (S)	S/M	OUTER (O)	INNER (I)	1/0
1) LD_{90}						
Adriamycin	0.13	31.0	239.0	2.5	40.0	16.0
Mitoxantrone	0.012	3.8	317.0	1.8	5.1	2.8
Menogaril	0.25	1.5	6.0	0.65	1.6	2.5
2) AC_{90}						
Adriamycin	0.06	10.0	167.0	0.71	11.9	16.8
Mitoxantrone	0.0039	0.85	218.0	0.54	1.5	3.0
Menogaril	0.12	0.49	4.1	0.18	0.42	2.3

1) Lethal dose to 90% of cells after a 2-hour incubation
2) Linear area under the curve between 10% to 100% survival

Assessment of Cardiac Damage Caused by Adriamycin

Adriamycin is a widely used cytotoxic chemical effective against many human tumors. It has a number of side effects such as leukothrombocytopenia, anemia, nausea, vomiting and alopecia -- all of which are reversible. Also it adversely affects the muscle of the heart: this is often not reversible.

We are studying the development of Adriamycin-induced cardiotoxicity using the cat and, more recently, the rabbit as the experimental animals. Nuclear magnetic resonance spectroscopy (MRS) is being used to measure ^{31}P spectra of the heart. Cardiac ejection fraction is determined using T_C-99 mm and an electrocardiogram is being recorded at regular intervals over a period of four months. Histologic sections of endocardium and epicardium will be made at 0 time, 2 weeks, and then 2, 3 and 4 months.

MRS, a non-invasive technique, may predict the onset of cardiotoxicity as well or better than current methods. This would allow the therapist to change to a less toxic drug or give a free radical scavenger, such as butylated hydroxyanisole, in an attempt to prevent or reverse myocardial damage. Since blood flow to the myocardium is considerably larger than to most tumors, one would expect the antioxidant given before Adriamycin to reach a higher concentration in the heart, and that a therapeutic gain would be achieved. The rise and clearance times of the two drugs in the heart and tumor would be important factors in choosing a chemical protector.

At the time of writing, eight animals have been operated. A phosphate marker consisting of a silastic tube containing 0.25M methylenediphosphonic acid is satured to the pericardium. The single turn copper coil can be placed directly beneath this tube and the animal's chest is then aligned so that the coil obtains signal only through this volume, at a depth beneath the skeletal muscle. This is accomplished using Robin Bendall's[1] depth pulse or the DRESS sequence of Bottomley[2]. Proton and phosphorus spectra have been obtained from all animals one week after operation. About 30 minutes are needed to collect a sufficient signal and we can resolve seven distinct peaks for phosphorus without gating the signal.

The use of ^{31}P MRS also may be useful in assessing other types of cardiac damage, such as coronary artery disease, cardiomyopathy due to chronic diabetes or changes in myocardial metabolism due to atherosclerosis.

This project was supported by a Grant from the Medical Research Council of Canada, the Cancer Research Society, and the Upjohn Company of Canada.

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SYNTHESIS AND REGULATION OF AMPLIFIED METALLOTHIONEIN-1 GENES IN VIVO*

J. KOROPATNICK**, *London, Ontario*

Gene amplification – a process in which a greater-than-normal complement of a specific gene or DNA sequence is generated within cells – has been proposed as a mechanism for controlling gene expression in eukaryotic somatic cells. It may be a marker for transformation and metastatic potential in tumor cells, and mediate some forms of drug resistance in those cells[1].

We have demonstrated specific in vivo amplification of the gene for mouse metallothionein-1 (MT-1) after exposure to cadmium – an inducer of expression of the gene[2]. A two- to three-fold increase in MT-1 gene copy number appears within 6 hours of induction, and persists for at least 3 weeks. We have explored this phenomenon to show that: (a) extra copies of the MT-1 genes are initially inactive in expressing gene product, but become active three days after induction; and (b) changes in nuclease sensitivity, which indicate an unusual, altered chromatin structure, accompany the changes in the gene's transcriptional activity. Therefore, the observed amplification appears to be part of a mechanism to regulate MT-1 gene expression in the mouse.

We are exploring the possibility that the gene amplification may be due to selective DNA replication and eventual cell division within a subpopulation of mouse liver cells with constitutively amplified MT-1 genes. *De novo* amplification events, difficult to reconcile with the rapid appearance of increased gene copy number, need not be invoked. Such mechanism would provide a role for gene amplification in the pantheon of "normal" mechnisms of gene regulation in mammalian cells in situ, and would provide insight concerning the generation of cells with a variety of amplified genes which appear in tumor cell populations in vivo.

This project was supported by the National Science and Engineering Research Council, and the Banting Foundation.

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*CS-103.

**Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London.

USE OF THE IMMUNE-DEFICIENT EMBRYONIC CHICK IN THE STUDY OF TUMOR PROGRESSION AND METASTASIS*

A.F. CHAMBERS**, *London, Ontario*

Metastasis continues to be one of the major reasons for failure of cancer treatment. We are using an experimental metastasis assay in the immune-deficient embryonic chick[1] to identify genetic properties that contribute to metastasis. Use of an immune-deficient host permits study of intrinsic metastatic properties in the absence of significant immune rejection of otherwise metastatic cells, and allows us to study separately these two important factors in metastasis – intrinsic metastatic ability and ability to escape immune destruction by the host[2].

Using this approach, we are analyzing the relationship between the human bladder cancer oncogene (H-*ras*) and metastasis. We have found that the *ras* oncogene can confer metastatic properties on NIH-3T3 cells[3]. We are examining the metastatic abilities of individual clones of *ras*-transformed cells, and observe heterogeneity of metastatic ability, with some clones being considerably better able to grow in the chick embryo than are others. Currently we are exploring the basis for this heterogeneity in metastatic properties.

This project was supported by a grant from the NCIC.

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*CS-150-1.

**Terry Fox (Ontario) Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario.

DYNAMIC HETEROGENEITY OF THE METASTATIC PHENOTYPE*

A.F. CHAMBERS** and J.F. HARRIS**, *London, Ontario*

The generation of heterogeneity is an important feature in the development of metastatic cells. We have proposed a dynamic heterogeneity model in which tumor cells acquire and lose certain metastatic properties[1,2]. We have used Luria-Delbruck fluctuation analysis of clonal populations of tumor cells in the quantitation of rates of generation of metastatic variants. We have found that one mechanism for the maintenance of a more highly metastatic phenotype is through a higher rate of generation of metastatic variants[3]. Currently we are extending this approach to the relationship between genetic instability and gene amplification, by clonal analysis of cells transformed with a temperature-sensitive oncogene.

This project was supported by a grant from the Medical Research Council of Canada.

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*CS-150-2.

**Terry Fox (Ontario) Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario.

EMBRYONAL CARCINOMA CELL MODEL OF EXPERIMENTAL METASTASIS[*]

J.F. HARRIS[**], *London, Ontario*

Mouse embryonal carcinoma (EC) cells provide an interesting model by which to investigate the basic biology of metastasis. When EC cells are injected into the tail vein of a mouse in an experimental metastasis assay, liver colonies are formed rather than lung colonies although the cells interact first with the lung capillary system. The liver colonization of EC cells is different from that observed in our previous studies using mouse fibrosarcoma[1] and melanoma[2] cells, which form experimental lung metastases almost exclusively.

We have proposed a dynamic heterogeneity model in which reversible change between non-metastatic and metastatic phenotypes occurs stochastically[1,2].

Initial data suggest that the dynamic heterogeneity model is applicable to the mouse EC cells metastasizing to the liver and that the effective rate of generation of metastatic variant cells is approximately $5x10^{-6}$ per cell per generation.

Alternative cancer therapy has been suggested which is based upon directing the differentiation of malignant to benign cells. This concept is being examined in relation to metastatic ability using mouse EC lines such as OTF9 which differentiate to benign endoderm-like cells upon exposure to retinoic acid. Monoclonal antibody against stage-specific embryonic antigen-1 (SSEA-1) antigen[3] serves as convenient marker to monitor the degree of differentiation. These studies are in progress.

This project is supported by a grant from the NCIC.

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[*] CS-151.

[**] Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London.

QUANTITATIVE STABILITY ANALYSIS OF HUMAN MONOCLONAL ANTIBODY PRODUCTION BY HETEROMYELOMA HYBRIDOMAS*

J.F. HARRIS** and J. KOROPATNICK**, *London, Ontario*

The instability of human monoclonal antibody production by hybridoma cells limits the usefulness of this important technology. To understand the mechanism of loss of antibody production, we have described the quantitative analysis of the stability of human monoclonal antibody production by hybridomas. Clones derived from fusion between the SHM-D33 heteromyeloma line and EBV-stimulated human lymphocytes were examined for antibody production using a fluorescent-labelling technique. The rate of generation of antibody-negative variants was calculated using Luria-Delbruck fluctuation analysis and, with respect to antibody production, some of the heteromyeloma hybridomas were found to be as stable as mouse hybridoma cells[1].

To define the mechanism of loss of antibody production, we have analyzed independent stable and unstable hybridomas using DNA probes. An *Alu* consensus sequence probe *(Blur8)*, which hybridizes to human but not mouse DNA, were employed to detect total human DNA, and human Ig gene probes were used to detect specific immunoglobulin genes. Preliminary results suggest that loss of the immunoglobulin genes accompanies antibody production loss, and instability of antibody production is correlated with the relative amount of human DNA in the hybridoma cells.

We are now addressing the following questions: (a) Is the amount of human DNA in antibody-producing heteromyeloma hybridoma cells a factor in maintaining stable antibody production? and (b) Is there a unique DNA sequence, or subpopulation of sequences, responsible for maintaining the stability of antibody production?

An answer to these questions would help to accurately predict the stability of antibody production in selected clones from the many that arise immediately after fusion of parent cells, and to select such clones for long-term culture and antibody production.

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*CS-151-1.

**Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London.

INVESTIGATION OF PHYSICAL RADIATION PARAMETERS*

D.J. DAWSON**, *London, Ontario*

The dose distribution in the penumbral region (edge) of therapeutic x-ray beams must be accurately established to avoid radiation-sensitive organs. This investigation used an extrapolation technique for one dosimetric system, namely ionization chambers of varying geometric configuration, to determine the corrected penumbral dose profiles for beam energies from Co^{60} to 31-Mv x-rays. The model proposed considers that there are two distributions in the penumbral region, namely the dose and photon-fluence distribution[1]. An ionometric technique has been developed to delineate the photon-fluence distribution. The differences between these distributions are analyzed to determine the lateral spread of the secondary electrons.

Theoretically, the dose spread functions associated with the measurement conditions are calculated and convolved with the corresponding photon-fluence distributions to determine theoretical primary penumbral dose distributions[2,3]. Good agreement between experiment and theory has been found over a wide range of geometric configurations.

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*Project 266. (Final Report)

**Head of Clinical Physics, OCTRF London Regional Cancer Centre; and Associate Professor of Radiation Oncology, and Sessional Lecturer of Physics, University of Western Ontario, London.

ADDITIONAL INVESTIGATIONS

Dr. H. Bush, Director of the London Regional Cancer Centre, reports on the following clinical research investigations:

CARCINOMA OF THE BREAST

Dr. P.J. Corbett is participating in the Stage I breast cancer study of the Ontario Clinical Oncology Group (OCOG).

LYMPHOMAS

The HD-4 and LY-3 studies of the NCIC continue to accrue patients. A local hematological oncology study group has been constituted for information exchange, generating research ideas, co-ordination of local or national clinical studies in the three local teaching hospitals, and compilation of local statistics on hematological malignancies.

OVARIAN CANCER

Patients are being entered into the OV-6 and OV-8 studies of the NCIC. However, patient accrual into the OV-7 study met with some difficulty because of the design of the study. Dr. A. Cheung completed a retrospective study on the efficacy of whole abdominopelvic irradiation as second-line therapy for residual epithelial ovarian cancer following chemotherapy.

In addition, Drs. L. Levin, H. Allen and E.R. Tustanoff are extending the original studies of CA125 antigen as a tumor marker in ovarian cancer with particular attention to intraperitoneal CA125 levels at the time of second-look laparotomy.

Dr. Levin, working with Dr. W.M. Hryniuk in Hamilton, has completed a dose-intensity analysis on chemotherapy used in the treatment of ovarian cancer. The analysis is being expanded to incorporate salvage chemotherapy regimen.

MYELOMA

Dr. A. Cheung is conducting a study on sequential, fractionated half-body irradiation as salvage treatment for patients with myeloma refractory to chemotherapy.

ENDOMETRIAL CARCINOMA

Dr. L. Levin is the co-principal investigator, with Dr. A.J. Dembo of the PMH, in an OCOG study to evaluate the efficacy of medroxyprogesterone and extended field irradiation in high-risk Stage I, Stage II and Stage III endometrial carcinoma.

GENITOURINARY CANCERS

Dr. A.R. Dar, under the sponsorship of Abbott Laboratories Ltd., is conducting a study on leuprolide and flutamide therapy for metastatic prostate carcinoma. In collaboration with five other cancer centres, Dr. Dar organized a provincial study on fallopian tube cancer. He is participating with Dr. P.J. Corbett in the BL-3 study sponsored by the NCIC.

DIETARY INTERVENTION STUDIES

Dr. L. Levin, and Dianne Goettler -- a research dietician -- are investigating gut-peptide hormone and prolactin release in response to a high and low-fat test meal in previous Stage I breast cancer patients and normal controls.

Drs. Kocha, Finley and Levin, and Dianne Goettler are investigating the correlation between dietary Vitamin A intake and the degree of tumor differentiation in new patients with non-small cell lung cancer.

NEUROONCOLOGY

Drs. J.G. Cairncross and D.R. Macdonald are studying the effects of steroids (dexamethasone) on the appearance of recurrent malignant gliomas on contrast-enhanced CT scans. An investigation is planned comparing MRI scanning and myelography in patients with epidural spinal-cord compression. A Phase III study in collaboration with Duke University, the University of North Carolina and the Northwestern University continues; this will compare chemotherapy with AZQ to BCNU following maximum feasible surgery and standardized radiotherapy for primary anaplastic gliomas. A collaborative Phase II study is underway comparing chemotherapy with AZQ to flundarabine in patients with recurrent malignant gliomas. Planned is a Phase II NCIC trial of trimetrexate in patients with recurrent malignant glioma.

RADIATION PHYSICS

Dr. D.J. Dawson is applying ionometric and convolution techniques to evaluate electron fluence effects in the regions of inhomogeneities of varying electron density for photon beams of high energy. This work is supported by the MRC.

SARCOMAS

Dr. Vivien Bramwell is national co-ordinator for the Canadian Sarcoma Group, which, in conjunction with the NCIC, has initiated a number of clinical trials. For advanced soft-tissue sarcoma, a new drug combination -- Adriamycin, ifosfamide and DTIC -- is being evaluated in a single-arm pilot study. In addition, a Phase II study of a new antifolite trimetrexate is in progress. A randomized Phase III protocol, undertaken in collaboration with the European Osteosarcoma Intergroup (EOI), compares a short, intensive, adjuvant treatment (Adriamycin/cis-platinum) with a longer, more complex multiagent regimen (modelled on Memorial Sloan-Kettering Hospital's T10). The Canadian Sarcoma Group is also considering the options for a randomized adjuvant study in soft-tissue sarcoma, and a pilot study of chemotherapy in spindle cell sarcomas of bone other than osteosarcoma (also to be performed in collaboration with the EOI) is about to be launched.

Ottawa Regional Cancer Centre

INVESTIGATION OF THE POSSIBLE ROLE OF OXYGEN RADICALS IN TUMOR PROGRESSION AND TUMOR-CELL HETEROGENEITY[*]

H.C. BIRNBOIM[**], S. KADHIM[†], B.F. BURNS[‡] and R.BOURRIER[***]
Ottawa and London, Ontario

We have continued our investigation into the mechanisms underlying the phenomenon of tumor progression and tumor-cell heterogeneity. In particular, we have been exploring the possibility that host cells, such as neutrophils and macrophages which commonly infiltrate solid tumors, are a source of factors that contribute to tumor-cell variability. Our specific hypothesis is that reactive oxygen species, produced by phagocytic cells in response to a variety of soluble and particulate stimuli, may cause alterations in the genetic information of tumor cells.

The experimental model is a fibrosarcoma line which is maintained by subcutaneous passage in syngeneic mice. This line has antigens which lead to its rejection in animals immunized against it. Our test for the induction of tumor-cell variants was the induction of immunoresistant cell lines, i.e., lines able to grow in immunosensitized animals. Groups of animals were injected with the pleotropic agent -- phorbol myristate acetate (PMA) -- which is a potent stimulator of reactive oxygen species by phagocytic cells in vitro. In animals, it has been used topically as a skin tumor promoter. Our results indicate that PMA is able to induce tumor-cell variants which exhibit an immunoresistant phenotype for at least six passages after the original PMA injections. Of 77 immunosensitized animals tested, 43 developed tumors at the sites of injection of tumor cells from PMA-treated animals whereas no tumors developed at the sites of injection of tumor cells from control animals. It has not yet been determined whether tumor production is related to oxygen radicals produced by phagocytes or some other action of PMA.

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[*] CS-104.

[**] Career Scientist, and Head of Experimental Oncology, OCTRF Ottawa Regional Cancer Centre, General Division; and Associate Professor of Medicine, and of Microbiology and Immunology, University of Ottawa.

[†] Research Assistant, University Hospital, London, Ontario.

[‡] Staff Pathologist, Ottawa Civic Hospital; and Assistant Professor of Pathology, University of Ottawa.

[***] NCIC Terry Fox Clerk.

MECHANISM OF OXYGEN-RADICAL DAMAGE TO CELLULAR DNA AND ITS ROLE IN TUMOR PROMOTION*

H.C. BIRNBOIM**, *Ottawa, Ontario*

Stimulation of phagocytic cells, such as neutrophils with various soluble and particulate stimulators, produces a variety of reactive oxygen species -- superoxide anion, hydrogen peroxide and others. The tumor-promoting agent, phorbol myristate acetate (PMA), is one of the most potent of these stimulators. In other cells, mitochondria, the auto-oxidation of many compounds and a variety of cellular enzymes also produce reactive oxygen species in lesser quantities. Our laboratory has been studying the effect, on cellular DNA, of oxygen species produced after PMA stimulation of human neutrophils.

Some years ago, we observed the appearance of DNA strand breaks and have been concentrating our efforts on understanding the mechanism involved. Surprisingly, it now appears that superoxide anion (a relatively non-reactive radical) may trigger a metabolic pathway that leads to the production of such breaks[1]. Although a much more reactive radical (hydroxyl radical) is present, it appears not to be involved. The production of breaks is markedly inhibited by metabolic poisons such as fluoride ion, 2-deoxyglucose and calcium ionophore A23187. The number of breaks also is markedly affected by vanadate -- a compound thought to act as a cellular phosphatase inhibitor, including phosphoprotein phosphatases. A property of these breaks is that, compared to radiation-induced breaks, they are repaired very slowly[2]. Our current hypothesis is that these breaks may be important in tumor promotion assiociated with inflammatory cells, such as mouse skin treated with PMA. We speculate that this class of slowly-repaired breaks may predispose cells to chromosome rearrangements or gene amplification associated with tumor promotion.

This project was supported by a grant from the Medical Research Council of Canada.

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*CS-104-1.

**Career Scientist, and Head of Experimental Oncology, OCTRF Ottawa Regional Cancer Centre, General Division; and Associate Professor of Medicine, and of Microbiology and Immunobiology, University of Ottawa.

ROLE OF DNA(CYTOSINE)-METHYLATION IN TUMOR PROGRESSION AND TUMOR-CELL BIOLOGY*

R.G. LITEPLO**, *Ottawa, Ontario*

It is now widely recognized that the progression of tumors from relatively benign to highly malignant states involves both genetic and epigenetic mechanisms. While many workers have investigated the influence of genetic mechanisms such as somatic mutation, chromosome rearrangement and gene amplification, increasing interest is being shown in the role of epigenetic mechanisms. One epigenetic mechanism believed to be involved in the progression of tumors and in the generation of tumor-cell heterogenity is alterations in the cytosine methylation of DNA.

It is well known that tumor cells exhibit major disturbances in methionine metabolism. We have altered the intracellular levels of specific metabolites of methionine, which are known to be involved in regulating DNA methylation. We have demonstrated that alterations in the levels of S-adenosylmethionine and S-adenosylhomocysteine inhibit DNA methylation and induce gene expression in certain established murine and human tumor cell lines. This suggests that the relative concentrations of these metabolites is (at least) one important factor in the regulation of DNA methylation (and consequently gene expression) within neoplastic cells.

Also we have examined the total genomic 5-methylcytosine content of a series of highly metastatic cell lines, which were derived from a poorly metastatic human melanoma tumor line. These malignant variants have substantially lower amounts of 5-methylcytosine within their DNA, an observation which further supports the hypothesis that alterations in the methylation of DNA may play a significant role in tumor progression.

This project was supported by a grant from the NCIC.

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*CS-108.

**Career Scientist, OCTRF Ottawa Regional Cancer Centre, General Division; and Assistant Professor of Medicine, University of Ottawa.

ADDITIONAL INVESTIGATIONS

Dr. G.E. Catton, Director of the Ottawa Regional Cancer Centre, reports on the following clinical research investigations:

In 1985, 339 patients were entered on clinical trials, and accrual in 1986 has increased to an average of 38 patients per month. Currently there are 58 active clinical research protocols.

TREATMENT OF BREAST CANCER

Investigators continue to enter patients into the National Surgical Adjuvant Breast Project (NSABP) protocols to determine the effect of adjuvant chemotherapy and hormonal therapy in breast cancer patients according to the age of the patient, as well as stage, and estrogen and progesterone status. Postmenopausal Stage II patients are entered on the NCIC MA.4 or the NSABP studies.

Surgeons and radiation oncologists are contributing patients to the Ontario Clinical Oncology Group Stage I breast carcinoma study, assessing the effectiveness of breast radiation following partial mastectomy and axillary dissection.

Postmenopausal patients with advanced breast cancer are eligible for participation in a study of Megace and tamoxifen. Those patients who have had no previous chemotherapy may be entered into the Phase II study of menogaril sponsored by the NCIC. Patients with advanced disease who have failed on or are not eligible for these regimens are candidates for a study comparing cyclophosphamide, Adriamycin and 5-FU to cyclophosphamide, Novantrone and 5-FU. Also recently activated is the multi-institutional Phase I study of high-dose epirubicin for patients who had failed anthracycline therapy, and the Phase I study of escalating epirubicin for patients who have failed therapy with cyclophosphamide, methotrexate, and 5-FU.

CURRENT STUDIES IN LYMPHOMA

The lymphoma group continues to contribute patients to the NCIC-sponsored trials, including the escalated BACOP/Septra study in poor-prognosis non-Hodgkin's lymphoma and the MOPP/ABV hybrid versus alternating MOPP/ABVD for advanced or recurrent Hodgkin's disease. A Phase II study of AT-125 as second-line therapy in poor-prognosis lymphomas is continuing to accrue patients, and the Phase II study of menogaril for patients with good prognosis lymphoma has been activated.

GASTROINTESTINAL PROTOCOLS

Accrual continues in the NSABP colon study, evaluating the postoperative portal-vein infusion of 5-FU and sodium heparin in patients with resectable adenocarcinoma.

Radiation oncologists are participating in a study assessing the effectiveness of whole abdominal radiation in resectable colon cancer.

Patients with locally advanced or disseminated gastric cancer are being entered into the Phase III study comparing epirubicin in combination with 5-FU versus 5-FU alone. In addition, the NCIC-sponsored study of systemic infusion versus bolus 5-FU for advanced colon cancer has been activated.

GYNECOLOGICAL/GENITO-URINARY TRIALS

Patients with ovarian carcinoma are being entered into the NCIC-sponsored trials. Patients with refractory malignant ascites are being entered into a locally initiated Phase II study of intraperitoneal cis-platinum.

Patients with superficial bladder cancers that have recurred after front-line intravesical therapy are candidates for a Phase I and pharmacological study of intravesical mitoxantrone. Patients with locally advanced bladder cancer are eligible for a study of intra-arterial cisplatin plus radiotherapy plus/minus cystectomy. Patients not eligible for this study may be entered in the local study of I.V. cis-platinum and disulfiram. In the near future, a Phase II study of I.V. weekly menogaril for locally advanced inoperable disease will be open for patient accrual.

Patients with advanced or residual local renal-cell carcinoma with no previous chemotherapy are eligible for entry into a Phase II study of escalating epirubicin. In addition, the study of mitomycin-C and metronidazole remains open for patients with metastatic, inoperable or locally recurrent renal cell carcinoma, with or without previous chemotherapy. The Phase II study of menogaril for advanced renal cell cancer is being reviewed for activation.

Patients with advanced prostatic cancer are eligible for the protocol comparing Megace in combination with stilbestrol versus stilbestrol alone. Soon to be activated is a Phase II study of epirubicin for disseminated or locally advanced prostatic carcinoma.

EAR-NOSE-THROAT STUDIES

Patients with ear-nose-throat malignancies are candidates for a study of lonidamine and radiotherapy. The Phase II study of mitoxantrone has been completed. In addition, accrual has been completed for the Warner-Lambert sponsored study assessing the effectiveness of trimetrexate in this disease category. A Phase I study of cisplatin, ara-C and pentoxyfylline is proposed.

LUNG CANCER

Radiation oncologists are assessing the effectiveness of adjuvant fractionated half-body radiotherapy in non-small cell lung cancer. Patients with limited squamous-cell lung cancer are being entered in a randomized study comparing radiotherapy with and without lonidamine. Patients with recurrent or metastatic disease are candidates for a Phase I study of acivicin plus cisplatin.

Patients with limited small-cell lung cancer are candidates for the NCIC study of early versus late radiotherapy combined with chemotherapy. The Phase II study of VP-16 and carboplatin is open to patients with extensive small-cell lung cancer.

The Phase II studies of trimetrexate and tiazofurin for advanced small cell and non-small cell disease have both met their accrual objectives. A study to determine the effectiveness of lonidamine and chemotherapy in advanced small cell and squamous-cell carcinoma is accruing patients.

All patients entered on small-cell lung cancer protocols are being considered for entry into a study to evaluate blood polyamine levels and plasma amino acid levels in relation to tumor burden.

MELANOMA

Patients with Stage I disease are eligible for the intergroup study of wide versus limited excision. Recently, the NCIC Phase II study of menogaril for advanced disease was closed. The NCIC proposal of a Phase I study of interferon is under review.

SARCOMA

The NCIC pilot study of Adriamycin/DTIC/ifosphamide in recurrent or metastatic soft-tissue sarcoma has been activated and is accruing patients. Several other Phase II studies, including trimetrexate in soft-tissue sarcomas and epirubicin in Kaposi's sarcomas, are being reviewed for future entry.

CENTRAL NERVOUS SYSTEM TUMORS

The Phase I study of intracarotid PCNU is now completed. Patients with "good-prognosis" glioblastoma are being entered on a study of front-line treatment, combining interstitial irradiation with external-beam irradiation and intracarotid BCNU, plus VM-26, plus cisplatin. In addition, a study has been activated for intra-arterial BCNU, cisplatin, VM-26, plus intravenous cytosine arabinoside and VM-26 as front-line or second-line chemotherapy for primary glioblastomas or low-grade gliomas. Patients with brain metastases may be entered on a study of radiotherapy plus lonidamine. Patients with primary brain lymphomas are eligible for a study using systemic PROMACE plus MOPP, in addition to intrathecal methotrexate, hydrocortisone and cytosine arabinoside.

Future studies include a Phase II trial of weekly menogaril after radiation for primary recurrent astrocytoma, and a Phase I-II study of intra-arterial interferon for either primary or metastatic brain cancer which has progressed after cranial irradiation, with or without previous chemotherapy. For patients with recurrent or progressive brain metastases following chemotherapy, a study is planned using intracarotid plus intravenous mitomycin-C, cisplatin and VM-26.

MISCELLANEOUS

In progress are active Phase I studies of weekly intravenous and oral menogaril, and cis-platinum plus disulfiram. Phase I studies are planned of didemnin-B, idarubicin by intermittent and daily oral administration. Other research proposed is to identify mechanisms by which cis-platinum containing regimens induce nausea and vomiting and thereby to identify better antiemetic regimens.

Also a double-blind study will be undertaken of lorazepam versus placebo for chemotherapy-induced emesis.

In addition to the major commitment to patient care and clinical research, oncologists of the Ottawa Regional Cancer Centre make a major commitment of time and energy to teaching and continuing education. They contribute to undergraduate training at the University of Ottawa Medical School through lectures, rounds and bedside teaching. In addition, they are responsible for ensuring excellence in the Royal College training programs in medical oncology and radiation oncology.

The Centre acts as a resource to the community. It trains community nurses in the techniques of chemotherapy administration and the management of the cancer patient undergoing treatment. As well, the Centre's library is a regional resource to the medical community on cancer-related matters and, on request, it provides resource materials to the public.

CLINICAL PHARMACOLOGY STUDIES

Dr. D.J. Stewart has conducted studies of cisplatin pharmacology and toxicity in collaboration with Drs. N. Mikhael and A. Nanji. It has been shown that the plasma pharmacokinetics of cisplatin are affected significantly by age, antiemetics, concurrent disulfiram, previous chemotherapy, concurrent chemotherapy, serum creatinine, creatinine clearance, serum albumin, serum uric acid, chloride, time of day of administration, cisplatin dose, patient sex and performance status. Response to cisplatin-based chemotherapy correlates with some pharmacokinetics parameters and with the use of some specific antiemetics (the response is lower after prochlorperazine).

The incidence of nephrotoxicity varied directly with some pharmacokinetic parameters, kidney concentrations of platinum, some types of concurrent chemotherapy, route of cisplatin administration (worse with hepatic-artery infusions), cisplatin dose, pretreatment serum creatinine, urea, uric acid, bilirubin and alkaline phosphatase. It varies inversely with pretreatment hemoglobin, serum albumin, serum chloride and creatinine clearance. Neurotoxicity correlated with some pharmacokinetic parameters and with serum albumin and with performance status. Ototoxicity correlated with some pharmacokinetic parameters, antiemetics and concurrent chemotherapy.

Drs. D.J. Stewart and R. Green continue with a number of mitoxantrone studies. Human autopsy studies have demonstrated that the heart retains high concentrations of mitoxantrone. Tumors in liver have higher mitoxantrone concentrations than do tumors in other organs, while tumors in the brain have the lowest. Separate studies have showed that, in patients with superficial bladder tumors, very little drug enters the blood stream after intravesical administration of mitoxantrone.

Pharmacokinetic studies of menogaril are continuing and studies with idarubicin will begin soon. Autopsy tissue distribution studies of VM-26 will also begin shortly.

MULTIMODALITY TREATMENT OF HYPERTHERMIA RADIATION AND CHEMOTHERAPEUTIC AGENTS IN CULTURED HUMAN AND ANIMAL TUMOR CELLS

Cell lines have been established from human melanoma and human glioma specimens. Some of these tumors are known to be radiation resistant and these cell lines are being established to investigate the potential of hyperthermia and drug treatment to increase radiation response and the overall response to these cell lines. To date, two glioma cell lines and two malignant melanoma cell lines have been established. The hyperthermia responses and radiation responses to these cell lines are being evaluated. Concerning the effect of chemotherapeutic agents on the two glioma cell lines, initial data indicate a large difference in responses between them.

We have obtained a large number of transformed tumorigenic mouse cell lines and have available the normal parental progenitor cell line. We are evaluating the radiation response to these cell lines and the ability to repair radiation damage. In addition, we will look at the effect of hyperthermia on these repair capacities with the objective of determining whether hyperthermia can sensitize radiation-resistant cell lines, which have an enlarged capacity to repair radiation damage.

PHYSICS AND HYPERTHERMIA

The Ottawa Regional Cancer Centre has developed a thermometry system, based on an IBM-PC interfaced to a Kiethly Data Acquisition System and using microthermocouple thermometry probes. An extensive in-house software package, which was developed for this system, is in its evolutionary stages and will be adapted to accommodate future needs. At present, the software reads 32 thermometry probes in one minute and controls the power of the microwave generator to a preset temperature on any one of the 32 probes. In addition, safety features ensure that if any probe exceeds a preset temperature the system will automatically shut down. This software is being improved to record a larger number of probes and possibly to carry out isothermal mapping in real time during the heating procedure. At present this equipment has been used to collect data in hyperthermia fields produced in phantom, in animals and in the Centre. The thermometry probe, which was developed at our Centre, can house 12 thermocouples within a sheath that fits inside a 19-gauge catheter. This thermocouple is being patented and we have filed for the status --"patent pending". This new multithermocouple probe, which has been used extensively in thermometry in animals and in human subjects, can deliver large volumes of thermometry data and thus give a good thermal profile of the tested tissue.

CLINICAL HYPERTHERMIA

A study in local hyperthermia and radiotherapy in recurrent, superficial malignancies, using the TAG MED microwave generator operating at MHz 2450 for the hyperthermia system, is carried out by: Drs. C.E. Danjoux, L.H. Gerig, G.P. Raaphorst, C. Cripps; and Miss S. Grimes and Mr. Z. Hauderowicz. Since December 1985, nine recurrent, superficial, measurable cancer lesions in eight patients were treated using the TAG MED 2450 MHz unit. Temperature at multiple points was measured using multiple-probe thermocouple arrays, inserted within and adjacent to the target volume. The lesions were treated by irradiation to 2000 cGY in 10 treatments over 2 weeks and hyperthemia (45°C for 1 hour) delivered twice weekly, 72 hours apart. Complete response was observed in 3 lesions and partial responses in 5. The treatment was well tolerated; there were no thermal burns or necrosis. During hyperthermia the main side effect was transient local discomfort, which was controlled by reducing the temperature by 1°C. Large thermal gradients, up to 7°C were recorded within the tumor. Temperature profiles were variable between patients and in the same patient from one session to another. In all cases, there was vascular compensation manifested by the need to increase the applied power to maintain the same temperature.

Thunder Bay Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. J.F. Kotalik, Director of the Thunder Bay Regional Cancer Centre, reports on the following clinical research investigations:

HEMATOLOGICAL MALIGNANCIES

We have continued to enter patients into the NCIC trial investigating the effectiveness of etidornate disodium as an adjuvant therapy in multiple myeloma. ikewise accrual has continued into the NCIC trial comparing standard BACOP with escalated BACOP in patients with poor prognosis non-Hodgkin's lymphoma. Also this Centre has been an active participant in the NCIC trial using 2-deoxycoformycin in the treatment of leukemic reticuloendotheliosis.

LUNG CANCER

The Thunder Bay Centre continues to participate in the North Central Cancer Treatment Group (NCCTG) trials of various mytomycin-C regimens for patients with metastatic non-small-cell carcinoma of the lung. Patients with locally unresectable disease are offered the opportunity to participate in a study, being directed by the Ottawa Regional Cancer Centre, which compares radiotherapy alone with combined radiotherapy of lonidamine. Also we continue active participation in the NCIC trial comparing early and late radiation therapy in association with chemotherapy for limited small-cell carcinoma of the lung. Accrual has begun into the NCIC study involving epirubicin for the treatment of extensive small-cell carcinoma of the lung.

GYNECOLOGICAL MALIGNANCIES

The Centre continues to participate in the NCIC ovarian trials and is comparing cyclophosphamide/cis-platinum versus cyclophosphamide/carboplatin as first-time treatment for advanced disease.

ADJUVANT CHEMOTHERAPY FOR BREAST CANCER

We continue to follow for survival and recurrence patients in the Ontario Clinical Oncology Group (OCOG) Stage I trial, which hopes to determine the effectiveness of breast irradiation following partial mastectomy and axillary dissection in node-negative carcinoma of the breast. Similarly we are following patients with node-positive disease who had entered the OCOG Stage II trial which compares intensive short-course chemohormonal therapy with standard extended chemotherapy. Currently patients, who are postmenopausal and node-positive, are being entered into the NCIC study which assesses tamoxifen with or without cytotoxic chemotherapy. Patients are being entered into the NCCTG trials, which involve varying combination of cyclophosphamide, methotrexate and 5-FU in patients with metastatic breast cancer. Patients who fail on such regimens are entered into a study comparing Adriamycin as a single agent with a combination including vincristine and mitomycin-C.

GASTROINTENSTINAL MALIGNANCIES

We are continuing participation in the NCCTG study, which tests various combinations of 5-FU, methotrexate, Leucovorin Calcium, and cis-platinum in metastatic colorectal carcinoma. An NCCTG protocol has been activated for non-measurable advanced carcinoma of the pancreas: It compares 5-FU with various 5-FU-containing regimens and we hope to continue our accrual into this study.

CENTRAL NERVOUS SYSTEM MALIGNANCIES

Under the auspices of the NCCTG, we are studying the value of combined modality therapy with the nitrosoureas, BCNU and PCNU in glioblastoma.

Hospital for Sick Children, Toronto

INTERMEDIATE FILAMENT PROTEIN MARKERS IN PEDIATRIC MALIGNANCIES*

R. BAUMAL**, M.J. PHILLIPS†, C.R. SMITH‡ and H. YEGER‡
Toronto, Ontario

Antibodies to the intermediate filaments cytokeratin, vimentin, desmin, neurofilaments and glial fibrillary acidic protein have proven useful for determining whether pediatric tumors arise from epithelium, mesenchyme, muscle, neurons or glial cells respectively. This is especially so in the case of undifferentiated tumors where light microscopic examination alone may not be conclusive. These antibodies, as well as a number of others, (antibodies to S-100 protein, actin and epithelial membrane antigen) have proven useful for distinguishing epithelial and myoepithelial cells in salivary gland tumors and for elucidating the histogenesis of these tumors[1,2]. In addition, antibodies to different forms of cytokeratin (epithelial and Mallory body) stained different components of rat salivary glands. This information was useful in understanding the histogenesis of human salivary gland tumors.

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*Project 463. (Final Report)

**Pathologist, Hospital for Sick Children, Toronto; and Associate Professor of Pathology, University of Toronto.

†Chairman, Department of Pathology, HSC; and Professor of Pathology, U of T.

‡Pathologist, HSC; and Lecturer of Pathology, U of T.

‡Research Associate, Department of Pathology, HSC.

Ontario Cancer Institute incorporating the Princess Margaret Hospital, Toronto

CLINICAL TRIALS SECRETARY FOR GASTROINTESTINAL TUMOR GROUP*

B.J. CUMMINGS** and G. DeBOER†
Toronto, Ontario

Studies continue of combinations of radiation and chemotherapy in epidermoid carcinomas of the anal canal, perianal skin and esophagus. The current protocols involve radiation and concurrent infusions of 5-fluorouracil, and have dropped mitomycin C which was included earlier. This amended protocol continues to produce two-year local control rates of about 60% for esophageal cancer, but, as yet, there are insufficient data to present results in other tumor sites.

We have completed accrual to the randomized trial comparing 5-fluorouracil plus folinic acid for patients with metastatic colorectal carcinoma. Preliminary analysis shows a significantly higher response rate to the folinic acid -- 5-fluorouracil combination, but survival data are not yet available[1].

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*Project 427. (Final Report)

**Radiation Oncologist, Princess Margaret Hospital; and Professor of Radiology, University of Toronto.

†Head, Department of Biostatistics, Ontario Cancer Institute; and Assistant Professor of Medical Biophysics, U of T.

CLINICAL TRIALS IN BREAST CANCER*

R.M. CLARK**, N.F. BOYD†, U. AMBUS‡ and
K.I. PRITCHARD‡, *Toronto, Ontario*

Three randomized controlled clinical trials are now in progress. These are:

1. A trial of ovarian irradiation and prednisone, following operation and radiotherapy undertaken for carcinoma of the breast, compared three forms of adjuvant therapy: ovarian irradiation and prednisone; ovarian irradiation alone; and no further treatment. The 756 patients, who were enrolled, now have been followed for at least eight years. In premenopausal women, aged 45 years or more, ovarian irradiation and prednisone significantly delayed recurrence, and prolonged survival. Further follow-up and analysis continue.

2. A trial is being conducted of postoperative treatment of breast cancer in premenopausal patients with histologically involved axillary nodes. This trial compares two treatments: (a) combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and ovarian irradiation plus prednisone; and (b) CMF alone. The trial is designed to determine if chemotherapy and hormonal therapy are complementary. To date 254 patients have been entered and 5 more patients are required to complete accrual. No results are available.

3. A trial was conducted of postoperative treatment of breast cancer in postmenopausal patients with histologically involved axillary nodes. This trial, which used tamoxifen as an adjuvant, was completed in April 1984 with 400 patients enrolled. Overall the five-year actuarial, relapse-free rates were 53% for patients receiving tamoxifen versus 40% for patients receiving no further treatment. As yet, there is no difference in overall survival between these two groups. Estrogen receptor status was known in 250 patients and progesterone

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*Project 446, including Projects 378 and 386. (Final Report)

**Radiation Oncologist, Princess Margaret Hospital, Toronto; and Associate Professor of Radiology, University of Toronto.

†Medical Oncologist, PMH; and Associate Professor of Medicine, U of T.

‡Surgeon, Toronto General Hospital; and Assistant Professor of Surgery, U of T.

‡Staff Physician, Women's College Hospital, Toronto; Lecturer in Medicine, U of T; Consultant in Medical Oncology, PMH; and Clinical Trials Scholar, National Cancer Institute of Canada.

receptor status in 241. Improvement in disease-free survival appeared to be confined to the receptor-positive subgroup. These results suggest that tamoxifen is useful in decreasing the recurrence rate in postmenopausal women with axillary-node-positive breast cancer following mastectomy. Benefit appears to be confined to women with receptor-positive breast cancer. Further follow-up and analysis continue.

INVESTIGATION OF A STEM-CELL MODEL OF A HUMAN TUMOR GROWTH*

R.N. BUICK**, *Toronto, Ontario*

We have used a combination of mathematical modelling and cell culture of human ovarian carcinoma ascitic tumor cells to investigate the hierarchical organization of tumor-cell populations.

The two systems we used were based, firstly, on a simple deterministic stem-cell model[1] and subsequently on a stochastic model[2]. The latter views the proliferation events within tumor-cell populations as a Galton-Watson branching process in which stochastic fluctuations lead to probability distributions in the numbers of each cell type around the mean values obtained from the earlier deterministic model.

To test the usefulness of the model for analyses of experimental data, we have used the sample means and variances from experimental distributions of colony sizes from cultured ovarian tumor cells as an initial basis for estimating some of the model's key parameters. These parameters were used as a starting point for simulations designed to generate distributions of colony and cluster sizes expected from the model for various specified parameter values. Comparisons of the experimental and simulated size distributions provide a preliminary test of the goodness of fit of the simulated distributions to the experimental ones. Simulations have also been used to test the sensitivity (of the colony and cluster size distributions) to change in the value of some of the key parameters. Of particular interest is the probability of self-renewal of tumor-stem cells, which may be the most importatnt single index of curability (potential for regeneration) of a tumor-cell population.

Based on the degree of agreement between simulations and actual experimental data, our work has reinforced the concept of cellular differentiation within human tumors, and the existence of minority-cell population with renewal potential. The quantitation of stem-cell frequency, based on extrapolation from the measured parameters of the model, provides a first estimate of this key parameter for human tumor[2].

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*Project 465. (Final Report)

**Senior Scientist, Ontario Cancer Institute, Toronto; and Associate Professor of Medical Biophysics, University of Toronto.

Toronto-Bayview Regional Cancer Centre

CULTURE-INDUCED CYTOTOXICITY FROM HUMAN PERIPHERAL LYMPHOID CELLS AND FURTHER CHARACTERIZATION OF HUMAN NATURAL KILLER CELLS*

J.J. RUSTHOVEN**, *Toronto, Ontario*

Natural killer cells (NKC) are large granular lymphocytes, which can kill tumor cells without prior exposure to the same target cells. While attempting to study killer cell suppressor activity in human peripheral blood lymphocytes (PBL), we found that a subpopulation of PBL generated NKC-like activity during culture in fetal-cell, serum-containing medium. This culture-induced cytotoxicity (CIC) was found in cell fractions of higher density than those containing NKC. The effector cells mediating this activity did not have the NKC-associated HNK-1 antigen or the OKT3 antigen but did display the OKM1 antigen on their cell surface. The latter was found on both precursor and mature killer cells. Other cells with OKT3 antigen could suppress this CIC. These killer cells appear to be distinct from NKC and lymphokine (interleukin-2) activated killer cells. Their specific role within the immune system is not yet known.

Recently we studied the volume regulation of NKC under hyptonic stress. It has been shown that T cells regulate their volume under such conditions whereas B cells do not. We found that NKC exhibit a regulatory volume reduction similar to thymocytes (mainly pre-T cells) and thus reduce their volume less than mature T cells but greater than B cells. This was true for NKC subpopulations defined by the presence of either the Leu-7 (HNK-1) or Leu-11 antigen. This functional characteristic supports the hypothesis that NKC may be derived from T cell precursors.

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*Project 468. (Final Report)

**Medical Oncologist, OCTRF Toronto-Bayview Regional Cancer Centre; and Assistant Professor of Medicine, University of Toronto.

University of Toronto

STUDIES IN ADULT LEUKEMIA*

M.A. BAKER**, *Toronto, Ontario*

Clinical Studies

The Toronto Leukemia Study Group recently completed two studies of acute myeloblastic leukemia (AML). In the first study, we have demonstrated the effects of inadvertent exclusions on the analysis of treatment results in this disease[1]. The complete remission rate in 272 patients with AML varied from 40% to 85% depending on exclusion criteria. Reports of treatment results must be examined in the light of potential exclusions for patients who were untreated, partially treated, were over the age of 70, had preceding myelodysplasia, other malignancy or cytotoxic chemotherapy. The second study included 125 patients with AML and demonstrated that patients in complete remission, who had received four months of consolidation, did not benefit from further remission maintenance chemotherapy[2]. We also showed that reinduction therapy, given at the time of immunological detection of imminent relapse, did not improve survival in this group of patients. We are conducting a Phase I-II trial of high-dose cytosine arabinoside using deoxycytidine infusion as a rescue technique. Laboratory studies suggest that deoxycytidine will reduce the toxic effects of cytosine arabinoside on normal marrow, but will permit the therapeutic effect on leukemia blast cells.

Laboratory Studies

Leukocytes in the granulocyte series demonstrate changes in membrane molecular structures with differentiation. Many of these changes can be recognized by monoclonal antibodies. Antigenic structures limited to very early stages of differentiation are potentially useful in separating leukemic or normal clonogenic cells from mixed-cell populations in the bone marrow. We have characterized the structure of one such molecular species[3] and hope to apply this information to autologous transplantation techniques for AML.

The pathophysiological behaviour of leukocytes in chronic myelogenous leukemia (CML) may be explained, in part, by aberrant sialylation of membrane glycoproteins or glycolipids. We have shown that a sialyltransferase specific for O-linked GalB1-3GalNAc oligosaccharide groups has increased expression in CML compared to normal granulocytes. We have now demonstrated increased activity of this enzyme in other myeloid leukemias and have observed that there is a burst of enzyme activity following stimulation of differentiation of leukemic cell lines[4]. Sialyltransferase may play a role in myeloid differentiation that is augmented in myeloid leukemias.

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*RA-200.

**OCTRF Research Associate; and Professor of Medicine, University of Toronto.

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ELECTRON MICROSCOPY OF THE UROTHELIUM IN PATIENTS WITH NON-INVASIVE BLADDER CANCER[*]

J.G. CONNOLY[**], E.P. deHARVEN[†] and W. HANNA[‡]
Toronto, Ontario

This research is aimed at defining methods to better assess the malignant potential of the mucosa in patients with non-invasive bladder cancer. These methods are based on advanced techniques in both transmission and scanning electron microscopy. Samples of the bladder mucosa from patients with bladder cancer and controls are examined under high-resolution scanning electron microscopy to characterize the ultrastructure of the luminal surface of the urothelial cells. Special emphasis is given to the structure and distribution of surface microridges, and the number, size and pleomorphism of the surface microvilli. In addition we are examining the level of expression of various cell surface and cytoplasmic antigens, using newer methods of immunoelectron microscopy including the use of monoclonal antibodies and colloidal gold specific marker. Also we are examining the common blood group isoantigens (A,B,H) and various surface glycoproteins.

We hope that these studies will enable us to recognize the early ultrastructural changes which precede the transformation of the bladder urothelium. These observations may lead us to recommend new diagnostic and prognostic tests for non-invasive bladder cancer. We seek to identify ultrastructural differences between benign, reversible hyperplasia and irreversible early neoplastic growth. Such tests may provide new ways to screen individuals who are at a high risk for bladder cancer. By recognizing early signs of transformation it may become possible, in some instances, to select and monitor patients who do not require aggressive intravesical chemotherapy. This is especially appropriate in patients with a history of low grade bladder cancer because many of the chemotherapeutic agents used in the treatment are themselves potent mutagens and are carcinogenic to the urothelium.

This project was supported by a grant from the Medical Research Council of Canada.

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[*] RA-201.

[**] OCTRF Research Associate; Professor of Surgery, University of Toronto; and Head, Division of Urology, Women's College Hospital.

[†] Professor of Pathology, and Director of Electron Microscopy Laboratory, U of T.

[‡] Director of Electron Microscopy Laboratory, WCH; and Assistant Professor of Pathology, U of T.

FACTORS AFFECTING URINARY MUTAGENIC LEVEL OF WORKERS WITH BLADDER CANCER*

J.G. CONNOLLY**, J.R. NETHERCOTT† and B.C.K. CHOI‡
Toronto, Ontario

This exploratory study aims to evaluate the utility of urinary mutagenicity screening to identify apparently healthy workers who have bladder cancers. Two urine samples from each of 40 bladder cancer cases and 40 hospital controls will be screened by the Ames bacterial tests. Test results will be related to the bladder cancer, simultaneously adjusted for confounding variables from epidemiologic questionnaires.

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*RA-201-1.

**OCTRF Research Associate; Professor of Surgery, University of Toronto; and Head, Division of Urology, Women's College Hospital.

†Associate Professor of Occupational Medicine, and Director of Occupational and Environmental Health Unit, U of T.

‡Assistant Professor of Epidemiology, U of T.

A RECESSIVE MUTATION INITIATES CANCER*

B.L. GALLIE**, *Toronto, Ontario*

Using retinoblastoma (RB) as an experimental model, we have shown that, in certain cancers, the earliest genetic changes initiating malignancy involve recessive mutations in tissue-specific genes. Malignancy develops only in the cell which also loses the remaining normal gene [1,2]. If the initial mutation is heritable, more than one individual tumor is likely to arise, resulting in bilateral retinoblastoma. Later survivors of RB are at risk of other tumors, particularly osteogenic sarcomas. We have shown that osteogenic sarcomas developing in RB patients or in previously unaffected individuals also result from unmasking of the recessive phenotype by loss of a normal allele at or near the RB locus[3]. Although every cell of individuals who have germline mutations in the RB gene is at risk of losing the normal allele, a generalized malignancy does not arise. We presume that the normal function of the recessive RB tumor gene is to promote terminal differentiation and to limit the extent of cell division in specific tissues.

Although the RB gene initiates malignancy when the normal allele is totally missing, other genetic rearrangements contribute to uncontrolled growth of the tumor[4]. We have characterized a specific rearrangement of chromosome 6p[5], seen in 60% of RB tumors. The gene N-*myc* is expressed by all RB tumors, because it is a normal product of proliferating fetal retina, but it is not expressed by adult nonproliferating retina[6]. The RB tumors, which proliferate most rapidly, show DNA amplification of N-*myc*, and presumably this contributes to the rapid growth.

The genetic locus for the RB gene is chromosome 13q14. Cloning of two genes within this region – esterase D[7] and an uncharacterized gene, 4.7R[8] – has revealed rearrangements in the DNA of some RB tumors. Since RB tumors can arise by deletional mutations involving large regions of chromosome 13 and many genes, and by mitotic recombinations affecting regions of chromosome 13 not adjacent to the RB gene[1], the 13q14 region near ESD and 4.7R must be explored carefully to identify the subregion most frequently involved. Then any genes in the region must be characterized with respect to tissue and developmental pattern of expression. Our preliminary work suggests that the 4.7R gene is distributed widely in tissue and shows no developmental regulation in retina; this suggests that it may not be the RB gene. However, the cloning of a gene close to the RB locus brings us much closer to cloning the gene that does initiate these tumors[9].

The RB gene is a member of a class of recessive tumor genes responsible for many specific malignancies. Of fundamental importance for understanding human cancer would be definitive analysis of this gene, its product and normal function, and the way in which mutations lead to malignancies.

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*RA-202-1.

**OCTRF Research Associate; and Associate Professor of Ophthalmology, University of Toronto.

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THE RELATIONSHIP OF PHEOMELANIN AND ULTRAVIOLET RADIATION IN CARCINOGENESIS*

H.F. HABERMAN** and I.A. MENON†, *Toronto, Ontario*

In collaboration with Dr. C. Cardella, the authors studied the incidence of malignancy in 523 Caucasian renal transplant patients in a Toronto centre and compared the results to other reports. Of these patients, 7.5% developed malignancy, and 72% of these were cutaneous. Cutaneous malignancy developed at a rate 3.2 times that expected in the general population; squamous cell carcinoma and basal cell carcinoma were seen 18.4 and 1.4 times as often. There was no statistical difference in the site of development of skin cancer between renal transplant patients and the general population. The former showed a propensity to develop multiple, more-aggressive skin cancers at an earlier age, especially on sun-exposed areas. The authors will undertake further prospective study to correlate these findings with other variables such as skin type and color, minimal erythemal dose and the amount and type of melanin.

Work continues on the contribution of melanin to the high incidence of skin cancer in people with red hair and light skin. Studies of the photochemical and photobiological reactions of melanins continue with a view to understanding the mechanisms of the ultraviolet (UV) radiation-induced cutaneous cancer. These studies show that UV irradiation of cells in vitro in the presence of pheomelanin produces cell damage. Our studies indicate that free radicals and reactive oxygen radicals produced during UV irradiation of pheomelanin may be involved in the detrimental effects that we reported previously.

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*RA-203.

**OCTRF Research Associate; Head of Dermatology, Toronto Western Hospital; and Associate Professor of Medicine, University of Toronto.

†Assistant Professor of Medicine and of Ophthalmology, U of T.

EVALUATION OF A NUCLEAR ESTROGEN RECEPTOR ASSAY FOR HUMAN BREAST CARCINOMA*

G.E. MOBBS**, *Toronto, Ontario*

A number of workers have reported that nucleus-associated estrogen receptor (ERN) may be a better indicator of the hormonal sensitivity of breast carcinomas than cytosolic ER and progesterone receptor (PgR) concentration. However, assay of ERN is not commonly used in the management of breast cancer, perhaps because the radioligand nuclear assay is more time-consuming and less accurate than the cytosolic assays. We have adapted a commercial enzyme immunoassay for ER (ER-EIA) for use with nuclear extracts of breast carcinoma specimens, and have examined the data obtained concerning cytosolic ER-EIA and standard steroid binding assays for cytosolic ER and PgR. Analysis of data from the first 136 tumor specimens show a significant correlation between the cytosolic ER concentration as measured by the EIA and steroid binding methods, and also between the $\log_{10}$ of the concentration of ER in the cytosolic and nuclear fractions assayed by the ER-EIA method. If 130 femtomoles (10^{-15})/mg DNA is used as a "cut-off" point to discriminate between high and low ERN values, 76 specimens had high ERN concentrations. Of these tumors 76% were positive or borderline for cytosolic ER as assessed by our routine steroid binding assay, and 74% were also positive or borderline for PgR. Sixty specimens had low ERN: 83% of these were negative for cytosolic PgR and 60% were also negative for ER. Thus high and low ERN values tend to be associated with positive and negative cytosolic PgR values respectively, although not all tumors fit this pattern. Positivity for cytosolic ER is not necessarily associated with high ERN values. However 92% of tumors with negative cytosolic ER had low ERN values.

In collaboration with Dr. W. Hanna, the EIA assay results are also being examined in relation to an immunohistochemical test for ER on frozen sections of the same tumor specimens. Follow-up of the patients involved will indicate which of these assays (or combination of assays) gives the most accurate prediction of hormonal sensitivity and/or prognosis.

This project was supported by a grant from Women's College Hospital Research Fund.

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*RA-205.

**OCTRF Research Associate; and Associate Professor of Surgery (Research), University of Toronto.

HORMONE RECEPTOR MECHANISMS IN THE DEVELOPMENT AND TREATMENT OF PROSTATIC NEOPLASIA*

G.E. MOBBS**, *Toronto, Ontario*

Following the observation that treatment with diethylstilbestrol (DES) induces the synthesis of progesterone receptor (PgR) in the androgen-sensitive R3327H (Dunning) rat prostatic adenocarcinoma, we have examined hormone-receptor profiles in other lines derived from the same tumor. These tumor lines differ from the H line in histopathological and growth characteristics, and in their sensitivity to androgens. In contrast to the well-differentiated and slow-growing H line, the AT line is anaplastic, fast growing and independent of androgen stimulation. Nevertheless, androgen receptors (AR) were detectable, and were able to bind to nuclear components, although preliminary experiments indicate that this binding may be of lower affinity than in the H line. The AT line does not contain ER or PgR. The G line is also poorly differentiated and fast-growing, but it is androgen sensitive. It contains amounts of AR, ER and PgR similar to the H line, but DES treatment does not stimulate a synthesis of PgR above the basal concentration.

These results suggest that, in this series of experimental prostatic carcinomas, androgen sensitivity may be associated with normal functional activity of AR, and differentiation may be associated with the ability to respond to estrogens rather than to androgens. We have not yet investigated the HI line – well differentiated, slow-growing and insensitive to androgens.

This project was supported by the NCIC.

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*RA-205-1.

**OCTRF Research Associate; and Associate Professor of Surgery (Research), University of Toronto.

RESEARCH UNIT OF THE DIVISION OF EPIDEMIOLOGY AND STATISTICS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION*

E.A. CLARKE**, N. KREIGER† and L.D. MARRETT‡
Toronto, Ontario

This Unit has been affiliated with the Department of Preventive Medicine and Biostatistics, University of Toronto, since 1978. It was established to conduct analyses using the cancer-data bases of the OCTRF, to assess the quality of these data, to provide cancer researchers with epidemiological and biostatistical assistance, to conduct or support cancer research projects, and to provide information which will enlarge the understanding of cancer by the general public and scientific community.

The following members of the Unit hold academic appointments at the University: Drs. E. Aileen Clarke, Loraine D. Marrett, and Nancy Kreiger. We continue to collaborate with the International Agency for Research on Cancer in studies of second primary cancers. In progress is the data collection phase of a case-control study of second primary cancers associated with chemotherapy, which was undertaken after a cohort study of second primaries in individuals given the diagnoses of Hodgkin's disease, testicular cancer, and ovarian cancer between 1964 and 1982. The cohort analysis revealed excesses of certain cancers possibly the result of chemotherapeutic exposures.

Analysis of 50 years of cancer mortality data for Ontario continues, including age-period-cohort modelling and assessment of the effects of therapy. In addition, the Unit is conducting population-based survival studies of Hodgkin's disease and testicular cancer by histologic cell type and other factors.

Dr. Clarke is collaborating with Dr. Stephen Walter of McMaster University in an evaluation of cervical cancer and dysplasia screening programs. Also she is collaborating with the Boston Drug Epidemiology Unit in a multicentre case-control study of breast cancer focussing on the roles of diazepam and alcohol as risk factors. In this study, neighbourhood and hospital controls are being interviewed to assess the effect of different control comparison groups. Dr. Kreiger is using the data from this study, with information from the Ontario Cancer Registry, to investigate risk factors associated with steroid receptor status in women with breast cancer.

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*Project 381.

**Head, Division of Epidemiology and Statistics, Ontario Cancer Treatment and Research Foundation, Toronto; and Associate Professor in the Department of Preventive Medicine and Biostatistics, University of Toronto.

†Head of Statistics, OCTRF; and Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T.

‡Epidemiologist, OCTRF; Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T; and Assistant Professor of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton.

Dr. Clarke continues her work with an international group of cancer registries under the sponsorship of the International Agency for Research on Cancer. A recently completed cohort study showed that survivors of testicular and ovarian cancer had 30% and 20% more second cancers respectively than the general population comparison group, and patients previously diagnosed with Hodgkin's disease had an 80% excess of such cancers. A case-control study is underway to elucidate the relationship of risk of some of these second cancers and cytotoxic therapy.

Dr. Marrett has continued to oversee the Toronto component of a case-control study of malignant melanoma – a collaboration between McMaster University, the University of Toronto and the OCTRF. Data collection will be complete early in 1987. In addition, she is analyzing data on the association between lower urinary tract tumors and analgesic use.

Drs. Marrett and Kreiger are conducting an investigation of risk factors for renal cell carcinoma, funded by the Ministry of Health of Ontario. This province-wide case-control study employs the Ontario Cancer Registry to ascertain cases.

With other members of a Canadian cancer registry-based research group, Drs. Kreiger and Marrett and Ms Hilditch have collaborated in a pilot study of thyroid cancer and irradiation. They have submitted a proposal to Health and Welfare Canada for funding for a full-scale, Canada-wide case-control study.

Dr. Marrett has been collaborating with Dr. W.E. Rawls of McMaster University in the design and analysis of studies of cervical cancer and sexually transmitted viruses.

Dr. Kreiger is completing her study of the epidemiology of fracture in postmenopausal women, funded by Health and Welfare Canada. She had developed a proposal for an epidemiological study of risk factors for osteogenic and Ewing's sarcomas in children and young adults.

Dr. Kreiger and co-workers in the Unit have completed the analysis data on cigarette smoking and endometrial neoplasia and will submit it for publication in 1987.

In collaboration with the City of Toronto Department of Public Health, Dr. Kreiger has completed the design, data collection, and analysis of an historical cohort study of an industrial-residential neighbourhood. This study used the Ontario Cancer Registry for cohort follow-up.

EVALUATION OF ELECTROMECHANICAL LARYNX*

V.S. DAYAL** and M.L.G. JOY†, *Toronto, Ontario*

Laryngeal cancer accounts for 1.8% of the cancers seen each year in Ontario. The conventional treatment for these lesions is surgery, radiation or a combination of both. Data from the Ontario Cancer Treatment and Research Foundation and from the American Cancer Society suggest that approximately 284 laryngectomies are performed each year in Ontario and 8000 in North America. The two major handicaps of this operation are an often poor voice, esophageal speech, and a permanent tracheostoma. Several devices and surgical procedures have been developed to improve the quality of speech, however, none has been very successful. The creation of a fistula between trachea and pharynx gives a reasonable speech but has been associated with fistula stenosis and aspiration.

We have built an endotracheal artificial larynx. After laryngectomy in experimental animals, this device, when placed in a surgically created large tracheopharyngeal fistula, prevents aspiration and provides an adequate airway.

During the past year, we have done further experiments to better understand the triggering mechanism of this device. A new, simpler and stable circuit has been developed for long-term patient use. A number of these devices were manufactured, and one is undergoing clinical trial in a patient.

A series of five articles describing this work has been published as a supplement in the *Annals of Otology, Rhinology and Laryngology*.

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*Project 451. (Final Report)

**Professor of Otolaryngology, University of Toronto.

†Associate Professor, Institute of Biomedical Engineering, U of T.

EPIDEMIOLOGY AND STATISTICS

CANCER INCIDENCE, MORTALITY AND TREATMENT IN ONTARIO

E.A. CLARKE, M.B.,B.S., M.Sc.*
N. KREIGER, M.P.H., Ph.D.** and
L.D. MARRETT, Ph.D.**
Toronto, Ontario

The Division of Epidemiology and Statistics is responsible for the adequate reporting of cases and the recording and compilation of data: One of the mandates of the Foundation under the Cancer Act. In pursuit of these objectives, the Foundation has maintained and improved a uniform case-recording system which was adopted by the regional cancer centres in 1947 and by the Ontario Cancer Institute incorporating the Princess Margaret Hospital (OCI/PMH) in 1957. The data from the regional cancer centres and the OCI/PMH are in machine-readable form from 1960 onwards. In addition to these records, the Foundation's computerized cancer-data base contains individual records on residents of Ontario who died from cancer since 1950; tabulations of deaths by sex, five-year age groups, and type of cancer from 1931 to 1985; individual records of patients diagnosed as having cancer in the Province between 1964 and 1984; individual records of hospital discharges on patients with cancer from 1964 to 1985; and pathology reports on specimens with cancer from 1972 to 1985. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

Most of the staff of the Division are located in the Head Office at 7 Overlea Blvd., but the Epidemiology Research Unit of the Division is located in the Department of Preventive Medicine and Biostatistics at the University of Toronto. Drs. Clarke, Kreiger and Marrett have cross-appointments in that department. This arrangement allows the staff of the Division to interact with other members of the epidemiological community and with medical and oncological colleagues.

In addition to the analyses of cancer incidence and mortality in the Province, the staff of the Division are involved in a number of other projects. Some are collaborative, using Ontario Cancer Registry data, with such agencies as the International Agency for Research in Cancer. Other studies are field studies conducted principally out of the Epidemiology Research Unit. Most of the case-control studies are supported by peer-reviewed grants.

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*Head, Division of Epidemiology and Statistics, Ontario Cancer Treatment and Research Foundation, Toronto.

**Epidemiologist, Division of Epidemiology and Statistics, OCTRF.

CANCER INCIDENCE AND MORTALITY

The Ontario Cancer Registry

In December 1986, the Ontario Cancer Registry produced 21 years of incidence data for the Province. The Registry now comprises information on more than 500,000 cases of cancer diagnosed in residents of Ontario between 1964 and 1984.

The Ontario Cancer Registry employs a unique system of registration, based on computerized record linkage on cancer cases collected routinely for other purposes and provided to the Foundation. The Registry receives more than 200,000 such records annually. The following province-wide data are routinely forwarded to the Registry:

1. Hospital discharges with a mention of cancer collected by the Hospital Medical Records Institute (HMRI) and supplied by the Ontario Ministry of Health; 100,000 computerized records per year.
2. Pathology reports with a mention of cancer submitted voluntarily by hospital pathology laboratories; about 35,000 paper records per year.
3. Reports on patients referred to the regional cancer centres and the OCI/PMH; 20,000 computerized records per year.
4. Deaths from all causes supplied by the Registrar General of Ontario; 65,000 computerized records per year.

Once source files are preprocessed, cancer incidence data are created in two major phases. First, sequential computer linkage of the source files is carried out to bring all records pertaining to an individual together. Then, a set of computerized rules called "case resolution" is applied to the linked records, to determine site of disease, histology, and date and method of diagnosis. Manual resolution is carried out routinely to deal with problems arising as a result of either linkage or case resolution.

To link together the large volume of data, the Foundation staff have developed a sophisticated computer record linkage system based on the Generalized Iterative Record Linkage System (GIRLS), designed by Statistics Canada in conjunction with the Epidemiology Unit of the National Cancer Institute of Canada. This system and the sequence of linkages are described in more detail in the section by Information Systems.

"Case resolution" consists of a set of computer programs, developed by Foundation staff, which apply medical logic to determine the appropriate site of disease, histology, and date of diagnosis. Cases may be supported by one or many source records; some cases may have only a pathology report or a death certificate; some may have several hospital discharges, several pathology reports, and several treatment centre reports. Obviously, the number of sources of records contributing to a case will determine the quantity and quality of data available on that cancer diagnosis.

The generation by the Foundation of cancer incidence data for Ontario is a joint effort between the staffs of the Division of Epidemiology and Statistics and Information Systems who, together, have developed these systems of record linkage and case resolution.

All incidence data presented are given according to the International Classification of Diseases, Ninth Revision (ICD9). While originally the Registry had coded the cancer sites according to the Eighth Revision of the ICD between 1964 and 1978, all records now have been converted to ICD9.

Cancer Incidence and Mortality, 1984

Currently the time lag between cancer diagnosis and publication of incidence data by the Ontario Cancer Registry is about two years. There is a delay until the essential data have been provided by the sources, then it is necessary to code pathology reports, edit and process the files as described. Thus, the most current cancer incidence data available are for 1984; these are presented in Tables I through IV and Fig. 1. Although last year's report gave cancer mortality data for 1984, we show them again in Tables III and IV, and Fig. 1, to facilitate comparisons between incidence and mortality for the same year.

Tables I and II give the frequencies by 5-year age group for each cancer site or group of sites, for males and females respectively, for 1984. Rank order is given in the far right-hand column to aid in quick identification of sites of most frequent occurrence. Cancer of the cervix was overreported in 1984 by about 10% because some cases of non-invasive disease were reported; this problem will be corrected later in 1987. Fig. 1 indicates the frequencies of cancer for selected sites and causes of death for both sexes in 1984. We have included the 10 most common sites, in terms of their sex-specific incidence frequencies; they are ordered according to their sex-specific incidence frequencies.

Tables III and IV present incidence and mortality rates by age group and site, for males and females respectively, for 1984. The rates for 15-year age groups and for all ages are age-adjusted, using the World Standard Population shown in Table VII. Description of the method of direct age-adjustment used here can be found in *Cancer Incidence in Five Continents,* vol. 4, by Waterhouse et al. Rates in the table have been "age-adjusted" to assist comparisons between the different areas. Adjustment for age is used to account for differences caused solely by differences in the age distribution in these areas. The rates shown in Tables III and IV can be compared with any other rates covering the same age span and using the same standard population for adjustment.

The "cumulative risk" (0-74), shown in the final column of Tables III and IV, is described in detail in *Cancer Incidence in Five Continents.* It is expressed per 100 and is a reasonable approximation to the risk to age 74 of being diagnosed with or dying of the given cancer. Thus, if the current age-specific rates for female lung cancer were to remain unchanged throughout her life, a girl born in 1984 would have about a 3% chance of receiving the diagnosis of lung cancer by

TABLE I

Annual Number of New Cases of Malignant Neoplasms in Males, by Site of Disease and Age at Diagnosis, Ontario 1984 (Provisional Data)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	1	0	0	1	1	4	4	5	18	37	48	69	69	77	57	100	10	501	8
Pharynx	146-148	1	1	1	2	2	0	0	2	6	8	18	27	23	10	6	13	0	120	
Esophagus	150	0	0	0	0	0	2	0	3	6	10	10	36	41	43	36	39	1	227	
Stomach	151	0	0	0	0	0	1	3	6	12	24	37	67	108	89	94	171	5	617	6
Intestine, except rectum	152,153	1	1	0	3	3	3	11	21	34	39	108	204	279	279	307	554	5	1,852	3
Rectum and anus	154	0	0	0	0	0	2	0	9	11	23	47	78	105	110	138	219	11	753	5
Pancreas	157	0	0	0	0	0	1	0	5	6	11	28	40	54	71	65	88	0	369	10
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	1	1	0	3	2	3	2	11	8	1	32	
Larynx	161	0	1	0	0	0	0	0	1	0	14	34	68	81	46	49	55	2	351	
Trachea, bronchus and lung	162	0	0	0	1	2	4	9	27	37	103	234	408	589	553	594	679	5	3,245	1
Bone	170	0	1	9	11	4	4	3	3	1	3	3	1	8	7	5	9	0	72	
Connective tissue	171	4	0	1	7	3	6	5	9	9	7	12	12	9	12	13	23	0	132	
Malignant melanoma of skin	172	0	0	0	1	10	14	24	27	35	28	42	28	41	37	20	41	2	350	
Prostate	185	0	0	1	0	1	1	0	0	5	13	46	181	308	474	593	1,074	4	2,701	2
Testis	186	1	0	1	9	19	53	36	22	16	2	5	7	5	3	2	2	1	184	
Bladder	188	0	0	0	0	3	5	9	11	27	29	82	144	185	185	234	377	1	1,292	4
Kidney and other urinary	189	7	2	0	0	2	0	5	19	10	25	48	63	77	77	59	71	5	470	9
Brain and other nervous system	191,192	13	9	6	12	13	11	23	13	14	20	25	31	44	35	37	26	0	332	
Thyroid gland	193	1	0	1	1	1	9	9	11	14	3	8	7	7	6	4	4	0	86	
Lymphosarcoma and reticulosarcoma	200	0	3	0	4	2	6	1	4	8	18	23	16	26	31	36	48	0	226	
Hodgkin's disease	201	2	1	9	11	18	17	15	16	8	8	11	5	6	9	12	9	1	158	
Other lymphomas	202	2	2	4	5	2	8	12	20	17	21	25	40	44	42	28	35	2	309	
Multiple myeloma	203	0	0	0	0	0	0	1	7	3	6	12	18	37	30	38	58	1	211	
Leukemia	204-208	33	20	6	14	11	9	15	10	21	24	29	41	64	66	77	132	3	575	7
Other and non-specific	Residual	13	5	1	6	10	8	20	26	34	75	112	166	246	222	242	396	10	1,592	
TOTAL	140-208[3]	79	46	40	88	107	168	205	278	353	551	1,050	1,759	2,459	2,516	2,757	4,231	70	16,757	

[1] ICD9 International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2] Rank order for 10 most common sites (or site groups).

[3] Excluding non-melanotic skin cancers (ICD9 number 173).

TABLE II

Annual Number of New Cases of Malignant Neoplasms in Females by Site of Disease and Age at Diagnosis, Ontario 1984

(Provisional Data)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	1	1	0	2	4	3	4	4	2	12	16	26	30	36	19	53	4	217	
Pharynx	146-148	2	0	0	0	0	1	0	3	5	3	7	10	14	4	4	6	0	59	
Esophagus	150	0	0	0	0	0	0	1	0	1	2	4	8	8	14	18	39	0	95	
Stomach	151	0	0	0	0	0	1	2	4	10	15	21	22	33	38	55	159	0	360	
Intestine, except rectum	152,153	0	0	0	3	1	5	8	21	30	53	98	156	215	270	299	700	5	1,864	2
Rectum and anus	154	0	0	0	0	0	1	2	10	13	24	26	59	77	82	96	199	2	591	6
Pancreas	157	0	0	0	0	0	0	3	2	3	5	12	28	38	50	53	132	1	327	
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	1	1	2	1	2	1	1	3	2	2	8	0	24	
Larynx	161	0	0	0	0	0	0	1	0	2	4	10	10	15	4	6	10	0	62	
Trachea, bronchus and lung	162	0	0	0	1	2	1	10	15	38	81	114	207	200	224	181	234	2	1,310	3
Bone	170	4	6	5	6	3	2	3	2	2	1	6	5	3	5	4	11	2	70	
Connective tissue	171	4	2	1	4	4	7	1	4	6	8	8	11	19	9	14	23	1	126	
Malignant melanoma of skin	172	0	0	1	6	9	30	32	29	32	35	39	33	30	32	23	54	5	390	10
Breast	174	0	0	0	2	6	30	97	197	331	390	435	551	540	493	439	854	4	4,369	1
Cervix uteri	180	0	0	0	2	8	38	41	61	42	38	28	32	42	50	36	45	3	466[4]	7
Body of uterus	182	0	0	0	0	1	1	14	7	24	35	80	145	215	200	118	128	3	971	4
Other and unspecified uterus	179,181	0	0	0	0	0	1	4	4	2	6	2	3	11	7	5	8	0	53	
Ovary and fallopian tube	183	0	2	2	6	12	15	20	20	43	33	58	95	90	85	65	105	1	652	5
Bladder	188	0	0	0	2	4	3	3	3	7	16	20	61	47	52	63	156	1	438	9
Kidney and other urinary	189	11	1	1	0	1	1	5	7	3	10	26	33	42	32	34	91	2	300	
Brain and other nervous system	191,192	9	11	5	6	7	12	16	15	25	19	29	29	38	32	33	36	0	322	
Thyroid gland	193	0	1	1	11	29	35	29	21	20	22	13	14	23	8	12	15	1	255	
Lymphosarcoma and reticulosarcoma	200	1	1	0	1	3	2	3	6	12	12	18	21	27	29	26	61	2	225	
Hodgkin's disease	201	0	2	1	17	15	20	4	13	8	4	5	5	9	7	6	7	0	123	
Other lymphomas	202	2	1	2	2	2	8	6	12	10	16	29	26	37	30	39	48	2	272	
Multiple myeloma	203	0	0	0	0	0	0	0	1	4	6	13	24	28	25	26	72	0	199	
Leukemia	204-208	28	4	9	7	12	6	7	11	17	21	17	29	48	52	49	136	3	456	8
Other and non-specific	Residual	19	3	1	7	8	8	27	25	33	56	92	113	166	181	192	527	7	1,465	
TOTAL	140-208[3]	81	35	29	85	131	232	344	499	726	929	1,227	1,757	2,048	2,053	1,917	3,917	51	16,061	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2] Rank order for 10 most common sites (or site groups).

[3] Excluding non-melanotic skin cancers (ICD9 number 173).

[4] Approximately 10% non-invasive cancer of the cervix.

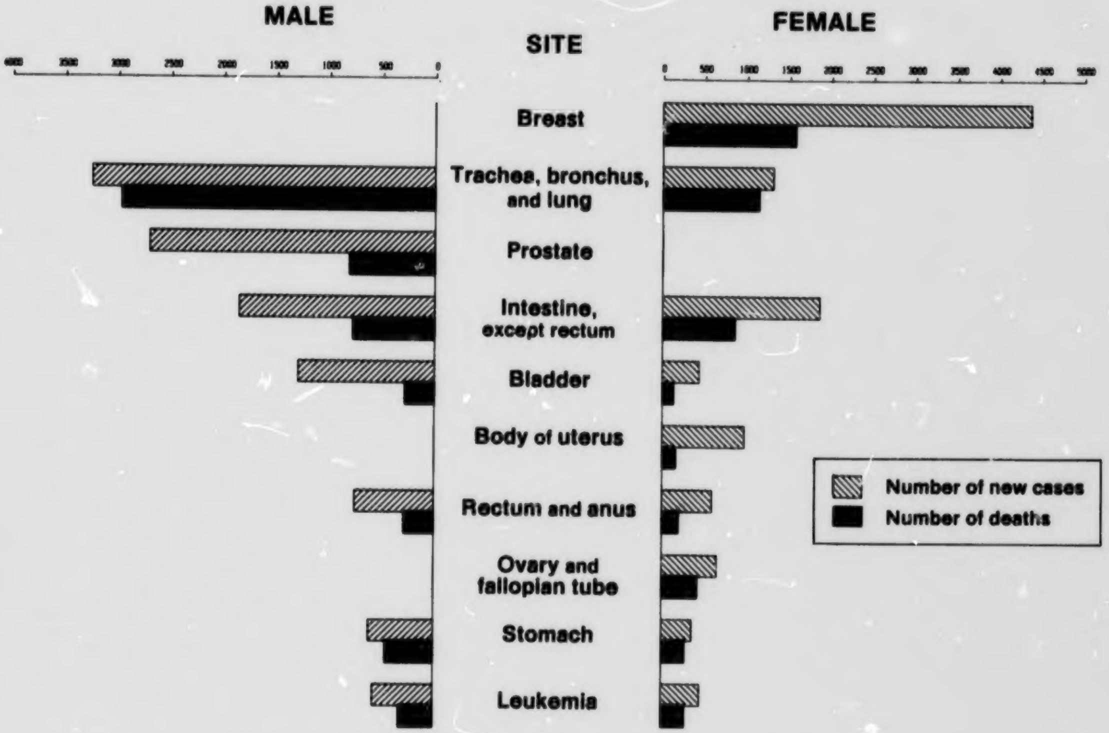

Fig. 1 New cases of, and deaths due to, malignant neoplasms, by sex and site of disease, for common cancers, Ontario 1984.

TABLE III

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Males, by Site and Age, Ontario 1984

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.1	0.5	3.1	21.2	44.9	75.4	9.5	1.08
		M	0.0	0.1	0.3	4.4	11.3	25.8	2.3	0.26
Pharynx	146-148	I	0.3	0.4	0.9	7.1	8.7	8.6	2.4	0.26
		M	0.0	0.0	0.1	2.4	7.3	5.3	1.1	0.14
Esophagus	150	I	0.0	0.2	1.0	7.4	26.4	28.7	4.3	0.55
		M	0.0	0.1	0.7	5.9	25.3	41.7	4.1	0.51
Stomach	151	I	0.0	0.1	2.3	17.3	63.8	129.7	11.4	1.31
		M	0.0	0.0	1.6	10.7	45.2	123.6	8.4	0.93
Intestine, except rectum	152,153	I	0.2	0.8	7.2	46.2	188.8	421.8	33.9	3.86
		M	0.0	0.3	1.9	16.2	77.9	218.8	14.3	1.57
Rectum and anus	154	I	0.0	0.2	2.2	19.8	76.6	164.8	13.6	1.61
		M	0.0	0.1	0.9	6.9	28.0	75.1	5.2	0.60
Pancreas	157	I	0.0	0.1	1.2	10.6	41.7	68.2	6.9	0.86
		M	0.0	0.2	0.9	10.8	50.8	95.5	8.3	1.00
Larynx	161	I	0.1	0.0	0.1	15.3	38.7	41.0	6.7	0.84
		M	0.0	0.0	0.0	2.6	14.9	21.9	2.2	0.28
Trachea, bronchus and lung	162	I	0.0	0.6	8.0	99.1	379.5	501.9	60.7	7.52
		M	0.0	0.2	4.1	81.9	345.9	546.5	55.1	6.71
Bone	170	I	0.9	1.7	0.7	1.1	4.4	7.5	1.5	0.13
		M	0.1	0.3	0.1	0.3	1.2	3.9	0.4	0.03
Malignant melanoma of skin	172	I	0.0	2.0	9.1	14.0	21.9	32.3	6.9	0.70
		M	0.0	0.3	1.8	3.7	7.0	14.5	1.9	0.19
Prostate	185	I	0.1	0.2	0.6	30.4	297.3	824.4	48.0	5.46
		M	0.1	0.0	0.1	4.4	57.7	404.0	14.0	1.11
Testis	186	I	0.2	6.7	7.5	1.9	2.2	1.3	3.6	0.28
		M	0.0	0.8	0.9	0.8	0.4	0.0	0.5	0.05
Bladder	188	I	0.0	0.6	5.2	33.7	131.2	289.3	23.7	2.76
		M	0.0	0.0	0.0	4.5	24.1	104.6	4.9	0.48
Kidney and other urinary	189	I	1.1	0.2	3.5	18.5	47.1	53.0	9.1	1.09
		M	0.0	0.0	1.4	6.1	22.9	32.5	3.9	0.48
Brain and other nervous system	191,192	I	3.1	3.1	5.1	10.6	25.4	18.8	6.9	0.73
		M	0.8	1.4	2.8	11.1	23.4	24.4	5.4	0.61
Thyroid gland	193	I	0.2	0.9	3.6	2.5	3.8	3.1	1.7	0.17
		M	0.0	0.0	0.0	0.3	0.9	3.1	0.2	0.02
Lymphosarcoma and reticulosarcoma	200	I	0.3	1.0	1.5	8.2	20.2	35.5	4.4	0.50
		M	0.0	0.3	0.7	1.0	6.2	18.2	1.3	0.12
Hodgkin's disease	201	I	1.1	3.9	3.9	3.5	5.8	7.1	3.2	0.29
		M	0.0	1.0	1.3	1.5	2.2	8.5	1.1	0.09
Other lymphomas	202	I	0.8	1.3	5.1	11.8	25.3	26.2	6.1	0.68
		M	0.0	0.5	1.2	3.6	20.3	40.1	3.5	0.43
Multiple myeloma	203	I	0.0	0.0	1.1	4.9	22.9	43.3	3.9	0.46
		M	0.0	0.0	0.3	3.5	14.4	39.7	2.7	0.29
Leukemia	204-208	I	6.6	2.9	4.9	13.0	45.1	100.0	11.7	1.14
		M	1.6	1.5	3.1	6.6	24.3	79.7	6.2	0.61
ALL SITES[4]	140-208[4]	I	17.9	30.6	89.2	451.1	1,687.7	3,210.3	313.0	30.70
		M	3.7	8.1	28.9	213.7	900.7	2,137.7	164.3	17.09

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15. pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

TABLE IV

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Females, by Site and Age, Ontario 1984

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.2	0.8	1.0	7.3	16.1	22.2	3.4	0.38
		M	0.0	0.0	0.1	1.7	4.2	8.8	0.8	0.09
Pharynx	146-148	I	0.3	0.1	0.9	2.7	4.2	2.5	1.1	0.12
		M	0.0	0.1	0.1	1.1	2.0	2.5	0.4	0.05
Esophagus	150	I	0.0	0.0	0.2	1.8	7.2	16.3	1.3	0.16
		M	0.0	0.0	0.3	1.9	7.0	19.2	1.4	0.15
Stomach	151	I	0.0	0.1	1.8	8.1	22.7	66.7	4.9	0.53
		M	0.0	0.1	0.8	4.1	18.5	55.6	3.6	0.39
Intestine, except rectum	152.153	I	0.0	0.8	6.4	40.8	143.1	292.4	26.2	3.05
		M	0.0	0.0	2.8	16.8	54.2	171.8	11.3	1.20
Rectum and anus	154	I	0.0	0.1	2.7	14.5	46.6	83.6	8.6	1.02
		M	0.0	0.3	0.6	3.9	13.4	36.1	2.7	0.29
Pancreas	157	I	0.0	0.0	0.8	5.8	25.8	54.9	4.4	0.53
		M	0.0	0.0	0.5	5.7	27.5	71.1	4.9	0.56
Larynx	161	I	0.0	0.0	0.3	3.3	4.7	4.2	1.1	0.12
		M	0.0	0.0	0.0	0.8	2.2	3.3	0.4	0.05
Trachea, bronchus and lung	162	I	0.0	0.3	7.0	53.6	112.7	96.7	21.5	2.68
		M	0.0	0.0	4.1	41.3	99.6	107.0	18.0	2.28
Bone	170	I	1.6	1.0	0.7	1.6	2.2	4.6	1.4	0.11
		M	0.3	0.3	0.1	0.0	0.4	2.1	0.3	0.02
Malignant melanoma of skin	172	I	0.1	3.7	9.6	15.3	16.0	22.9	6.9	0.67
		M	0.1	0.3	1.5	2.1	2.9	5.7	1.1	0.11
Breast	174	I	0.0	3.1	68.3	191.0	274.3	356.5	73.6	7.90
		M	0.0	0.4	12.4	60.4	111.3	170.5	24.8	2.83
Cervix uteri	180	I	0.0	3.9	14.7	14.1	24.0	18.6	8.3	0.86
		M	0.0	0.4	4.2	5.8	10.9	20.1	3.1	0.33
Other uterus	179.181.182	I	0.0	0.2	5.9	35.6	105.6	57.9	17.1	2.20
		M	0.0	0.1	0.2	1.9	17.8	32.1	2.6	0.32
Ovary & other uterine adnexa	183	I	0.4	2.8	9.0	24.7	45.0	44.3	11.1	1.26
		M	0.1	0.2	2.5	12.7	37.2	45.7	6.7	0.80
Bladder	188	I	0.0	0.8	1.4	12.5	29.5	65.1	6.3	0.72
		M	0.0	0.0	0.3	1.6	6.5	34.1	1.6	0.15
Kidney and other urinary	189	I	1.6	0.2	1.5	9.2	20.1	38.7	4.8	0.50
		M	0.3	0.2	0.2	3.7	10.1	18.6	2.6	0.23
Brain and other nervous system	191.192	I	2.8	2.1	6.0	10.7	19.1	15.5	6.1	0.62
		M	1.7	0.6	2.7	6.6	12.8	15.1	3.6	0.37
Thyroid gland	193	I	0.2	6.2	7.1	7.2	8.1	6.0	4.8	0.42
		M	0.0	0.0	0.0	0.6	2.4	4.4	0.4	0.05
Lymphosarcoma and reticulosarcoma	200	I	0.2	0.5	2.3	7.0	15.2	25.8	3.6	0.39
		M	0.0	0.1	0.4	0.9	3.4	11.1	0.8	0.08
Hodgkin's disease	201	I	0.3	4.5	2.6	2.0	4.1	3.2	2.4	0.20
		M	0.0	0.5	0.6	0.5	3.3	2.6	0.7	0.08
Other lymphomas	202	I	0.6	1.0	2.9	9.8	19.4	20.6	4.6	0.53
		M	0.0	0.0	1.3	2.7	10.3	26.7	2.1	0.23
Multiple myeloma	203	I	0.0	0.0	0.6	5.6	14.6	30.0	2.9	0.33
		M	0.0	0.0	0.2	1.6	8.2	23.5	1.5	0.15
Leukemia	204-208	I	4.8	2.1	3.8	9.3	27.6	56.8	7.7	0.73
		M	1.1	1.8	2.1	4.0	17.7	42.4	4.2	0.44
ALL SITES[4]	140-208[4]	I	16.8	37.5	168.0	533.0	1,115.9	1,642.5	258.1	25.25
		M	4.7	6.0	40.9	197.5	544.8	1,105.8	111.1	11.88

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15, pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

age 74. Of course, if age-specific rates continue to rise, the cumulative risk will increase also.

Cancer Mortality, 1985

The most current cancer mortality data available are for 1985; these were provided by the Office of the Registrar-General of Ontario. Figs. 2 and 3 show the frequencies of death due to malignant neoplasms of all types relative to other major groups of causes of death. Tables V and VI give the numbers of cancer deaths by age group at death and site; the same format and groupings are used in Tables I and II for cancer incidence.

Populations

Table VII shows sex- and age-specific population data for Ontario for the years 1984 and 1985, and for the "world standard". The 1984 and 1985 Ontario populations, which are postcensal estimates, are provided for those who would like to calculate age-specific cancer incidence and mortality rates from data tabulated in the previous sections. The world population is an artificial standard, frequently used in the calculation of age-adjusted rates. The Ontario population data are provided by Statistics Canada, and the world population is taken from *Cancer Incidence in Five Continents.*

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1984-85, there were 71,158 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.6% of all hospital separations and 1,097,342 days of hospital care. The average length of stay for cancer patients declined from 16.9 days in 1972 to 15.2 days in 1984-85*.

New Cancer Registrations

In the last decade, the number of new cases registered at the regional cancer centres and the OCI/PMH has increased by 49% from 14,698 cases to 21,895 (Table VIII). To assess the significance of these changes over time, one must take into account the introduction in 1979 of the *International Classification of Diseases, Ninth Revision,* which separated the categories – in situ carcinoma and neoplasms of uncertain behaviour – from malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients

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*Hospital Statistics 1984-85 published by the Ontario Ministry of Health.

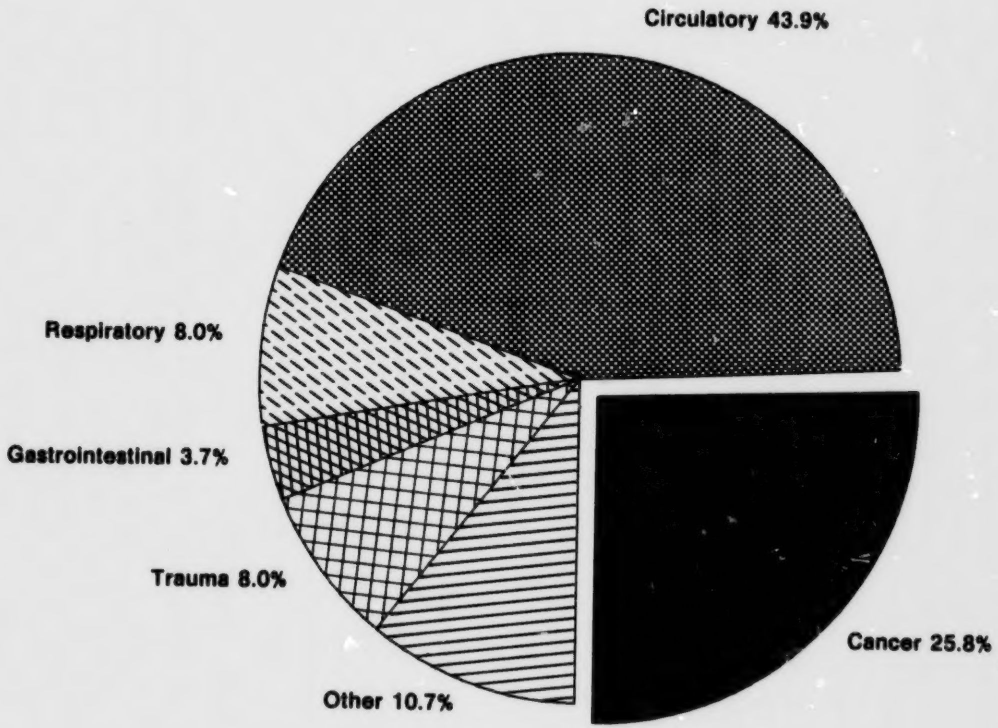

Fig. 2 Percentage distributions of major causes of death in males, Ontario 1985

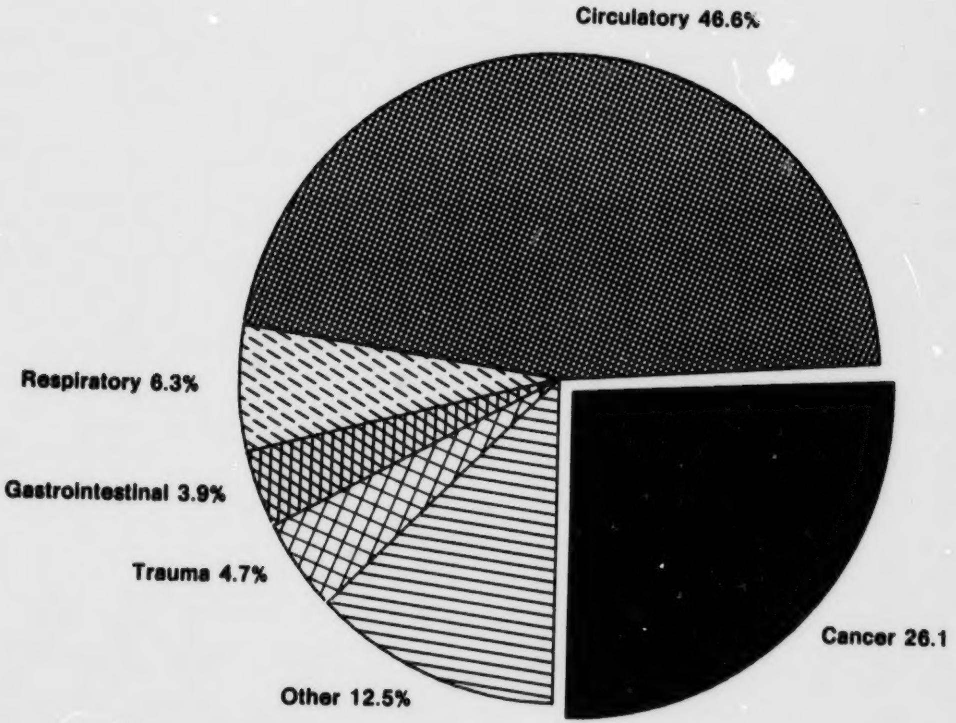

Fig. 3 Percentage distribution of major causes of death in females, Ontario 1985

TABLE V

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario 1985

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	1	0	1	2	5	16	21	20	19	18	39	142	13
Pharynx	146-148	0	0	0	0	1	0	0	0	7	7	4	11	13	14	9	10	76	
Esophagus	150	0	0	0	0	0	0	0	2	6	11	19	39	45	38	46	62	268	9
Stomach	151	0	0	0	0	1	1	1	5	5	12	26	32	59	63	73	168	446	5
Intestine, except rectum	152,153	0	0	0	0	0	1	3	6	14	22	32	87	95	114	151	298	823	3
Rectum and anus	154	0	0	0	0	0	0	0	1	7	5	11	28	32	44	42	115	285	8
Pancreas	157	0	0	0	0	0	1	1	2	12	15	24	35	61	71	85	154	461	4
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	1	0	1	0	1	0	2	2	2	4	13	
Larynx	161	0	0	0	0	0	0	0	2	0	2	7	20	18	19	22	24	114	16
Trachea, bronchus and lung	162	0	0	0	0	2	0	4	15	28	66	176	344	483	518	510	773	2,919	1
Bone	170	0	0	1	2	3	4	1	1	0	0	0	1	3	1	1	4	22	
Connective tissue	171	0	0	0	1	1	2	2	2	1	3	1	4	3	1	4	8	33	
Malignant melanoma of skin	172	0	0	0	1	1	0	5	6	11	6	10	13	22	14	12	23	124	15
Breast	175	0	0	0	0	0	0	0	0	0	0	0	1	1	2	3	4	11	
Prostate	185	0	0	0	0	0	0	0	0	0	3	3	26	65	110	174	526	907	2
Testis	186	0	0	0	0	2	2	4	2	2	0	1	1	3	1	1	2	21	
Bladder	188	0	0	0	0	0	0	0	1	1	1	13	17	27	43	57	140	300	7
Kidney and other urinary	189	1	0	0	0	0	1	3	7	2	8	18	27	21	27	35	51	201	11.5
Brain and other nervous system	191,192	3	2	2	3	6	9	6	11	10	11	14	35	41	30	31	26	240	10
Thyroid gland	193	0	0	0	0	0	0	0	0	0	1	1	1	0	1	3	6	13	
Lymphosarcoma and reticulosarcoma	200	0	0	1	1	1	1	0	1	3	1	3	5	4	15	7	20	63	
Hodgkin's disease	201	0	0	0	1	8	2	2	2	3	1	2	3	5	5	6	3	43	
Other lymphomas	202	1	1	0	4	2	2	4	3	6	15	12	23	18	32	34	44	201	11.5
Multiple myeloma	203	0	0	0	0	0	0	0	2	3	4	5	9	17	23	26	44	133	14
Leukemia	204-208	4	2	4	4	8	8	9	4	12	10	20	19	26	46	63	127	366	6
Other and non-specific	Residual	2	0	1	2	4	3	4	5	14	27	48	104	147	106	150	327	944	
TOTAL	140-208[3]	11	5	9	19	40	38	50	81	150	236	467	906	1,231	1,359	1,565	3,002	9,169	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for sites with more than 100 deaths.
[3] Omitted are 37deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VI

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario 1985

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	0	0	2	1	3	9	8	7	10	6	33	79	
Pharynx	146-148	0	0	1	0	0	0	0	0	0	3	7	1	5	2	3	6	28	
Esophagus	150	0	0	0	0	0	0	0	0	0	0	2	5	8	12	17	58	102	16
Stomach	151	0	0	0	0	0	0	1	3	2	3	10	20	26	23	43	140	271	7
Intestine, except rectum	152,153	0	0	0	0	0	1	4	7	10	16	33	61	72	106	114	412	836	3
Rectum and anus	154	0	0	0	0	0	0	0	2	3	6	9	13	19	23	35	111	221	8
Pancreas	157	0	0	0	0	0	0	2	5	2	6	16	41	40	69	72	182	435	5
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	6	10	
Larynx	161	0	0	0	0	0	0	0	0	1	0	1	1	6	4	2	6	21	
Trachea, bronchus and lung	162	0	0	0	0	0	1	4	8	40	48	87	148	201	243	200	302	1,282	2
Bone	170	0	0	3	1	0	0	0	0	0	0	0	1	0	1	2	4	12	
Connective tissue	171	0	0	0	0	0	1	2	0	3	2	4	2	3	3	6	9	35	
Malignant melanoma of skin	172	0	0	0	1	0	1	6	3	10	7	7	9	7	8	6	22	87	
Breast	174	0	0	0	0	1	4	20	42	61	91	146	169	225	193	213	456	1,621	1
Cervix uteri	180	0	0	0	0	1	6	8	15	10	17	13	12	20	19	23	34	178	12
Other uterus	179,181,182	0	0	0	0	0	0	0	1	2	8	5	9	22	29	25	87	188	10
Ovary and fallopian tube	183	1	0	0	0	2	3	2	4	20	20	33	46	64	66	74	126	461	4
Bladder	188	0	0	0	0	0	0	0	0	0	1	2	9	6	10	14	80	122	15
Kidney and other urinary	189	0	1	2	1	1	1	1	1	0	3	4	10	13	21	23	56	138	14
Brain and other nervous system	191,192	1	1	2	2	4	5	6	6	7	10	19	22	33	26	28	38	210	9
Thyroid gland	193	0	0	0	0	0	0	0	0	0	2	0	2	3	2	5	15	29	
Lymphosarcoma and reticulosarcoma	200	0	2	0	0	0	0	0	0	0	3	2	4	5	6	8	30	60	
Hodgkin's disease	201	0	0	0	0	2	1	2	0	0	1	2	2	2	4	4	4	24	
Other lymphomas	202	0	0	2	0	0	1	4	0	4	4	11	11	19	29	27	74	186	11
Multiple myeloma	203	0	0	0	0	0	0	0	2	0	3	4	15	11	20	33	69	157	13
Leukemia	204-208	2	3	7	4	6	6	5	8	12	10	10	13	25	27	37	124	299	6
Other and non-specific	Residual	2	2	0	2	3	3	7	8	16	14	42	96	103	106	124	437	965	
TOTAL	140-208[3]	6	9	17	11	20	34	74	117	204	282	479	731	945	1,063	1,144	2,921	8,057	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for sites with more than 100 deaths.
[3] Omitted are 19 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VII

World Standard Population and Estimated Population 1984 and 1985, of Ontario (In Thousands)

AGE GROUP	WORLD STANDARD[1]	ONTARIO, 1984[2]		ONTARIO, 1985[2]	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	316.4	302.9	322.8	308.5
5-9	10.0	309.1	294.4	309.2	295.1
10-14	9.0	336.3	317.8	331.8	313.5
15-19	9.0	370.5	352.9	359.7	342.3
20-24	8.0	423.6	416.1	429.4	418.8
25-29	8.0	383.7	396.4	395.1	404.9
30-34	6.0	357.0	371.5	365.4	381.4
35-39	6.0	341.2	343.8	354.1	359.1
40-44	6.0	274.1	272.6	283.8	282.1
45-49	6.0	239.0	237.1	242.7	241.3
50-54	5.0	236.3	233.3	234.4	232.4
55-59	4.0	222.6	233.1	225.2	233.3
60-64	4.0	197.0	221.6	201.2	227.1
65-69	3.0	141.4	167.2	145.9	172.5
70-74	2.0	113.5	144.0	117.8	149.8
75+	2.0	133.5	237.6	139.0	246.4
TOTAL	100.0	4,395.2	4,542.3	4,457.5	4,608.5

[1] Waterhouse, John et al (eds). Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p.673.

[2] Source: Statistics Canada.

TABLE VIII*

New Cancer Cases Registered by Treatment Centre, 1976-1985[1,2]

CENTRE	YEAR OF REGISTRATION									
	1976	1977	1978	1979	1980	1981	1982*	1983	1984	1985
Hamilton	2,254	2,353	2,493	2,594	2,507	2,537	2,688	2,780	2,782	3,498
Kingston	916	988	1,040	999	984	997	1,073	1,226	1,195	1,238
London	2,460	2,344	2,488	2,537	2,583	2,529	2,563	2,748	2,950	3,080
Ottawa	1,631	1,759	1,902	1,997	2,078	2,190	2,248	2,573	2,847	2,929
Thunder Bay	399	365	412	369	401	462	444	435	506	505
Toronto-Bayview	—	—	—	—	441	504	816	1,251	1,826	2,264
Toronto, PMH	6,158	6,462	6,960	6,911	7,057	7,320	7,012	7,332	7,171	7,328
Windsor	880	843	854	898	813	907	858	960	1,038	1,053
TOTAL	14,698	15,114	16,149	16,305	16,864	17,446	17,702	19,305	20,315	21,895

*Provisional (transition period — see text)

[1] Excludes carcinoma of cervix in situ.

[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

with skin cancer as having only two lesions – basal-cell or squamous-cell cancer – and not as having multiple cancers of the same histology in different body sites. The distribution by cancer centre of the numbers of in situ lesions, neoplasms of uncertain behaviour and multiple skin cancers is shown at the foot of Table IX.

This increase in the number of cases seen at the regional cancer centres can be attributed in part to the greater occurrence of cancer in the population during the last decade. This increase represents a combination of an increase in population in Ontario, which is also aging, and an increase in smoking-related cancers. It is anticipated that these trends will continue, with an expected annual increase in the absolute number of new cases of cancer requiring treatment.

In Table IX, for 1985, the major sites of newly registered cancers at these centres were lung, bronchus and trachea (15.8%), and breast (17.3%), followed by non-melanoma of the skin (10.7%). Of the 19,870 cancers seen for the first time at one of the regional cancer centres or the OCI/PMH, 16.2% were seen in Hamilton, 5.1% in Kingston, 13.4% in London, 13.4% in Ottawa, 2.4% in Thunder Bay, 10.2% at Toronto-Bayview, 4.7% in Windsor, and 34.6% at the Princess Margaret Hospital.

It should be noted that a "new case" registered at a Foundation's regional cancer centre refers to a case of cancer seen for the first time during that year at any one of the Foundation centres. If a case is seen at two cancer centres in the same year, the case is recorded as seen only by the first centre (1.6% of cases were seen at more than two centres in the same year).

The location of the peripheral clinics associated with the regional cancer centres and the OCI/PMH, and the type of outreach program, determine the referral pattern to each (Table X). Thus, in Lambton County, of the 282 cases resident in the county, 275 were referred to the London Centre and only a small number to other centres. On the other hand, in Halton County, of the 454 cases resident in Halton County, 270 were referred to the Hamilton Centre, 169 to OCI/PMH and 12 were referred to the Toronto-Bayview Centre. From the Province of Quebec, 459 residents were referred to Foundation centres; most were seen at the Ottawa Centre. Additional 130 residents of other provinces were seen in Ontario, principally at the OCI/PMH. Of the 172 residents of the USA and other countries treated in Ontario, most were seen at the OCI/PMH, and the Toronto-Bayview and Kingston Centres.

The data in Tables VIII through X are marked "provisional", since implementation of the Patient Care Management System in the centres from which these are extracted, is not yet complete. However, we anticipate that the final data will differ only slightly from those presented here.

Seminar in Cancer Epidemiology

The Foundation held its first full-day Cancer Epidemiology Seminar in 1986. The program was held at the Ontario Hospital Association and those in attendance included epidemiologists, graduate students, residents in community health, re-

TABLE IX*

New Cancer Cases Registered by Site of Disease and Treatment Centre, 1985

SITE OF DISEASE	ICD9[1] NUMBER	TREATMENT CENTRE								TOTAL	
		Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	Number	Per Cent
							Bayview	PMH			
Lip	140	19	17	22	9	2	4	18	9	100	0.5
Tongue	141	18	7	19	29	2	19	62	6	162	0.8
Rest of mouth	142-145	40	12	37	36	9	35	127	17	313	1.6
Pharynx and tonsil	146-149	32	10	43	40	2	34	150	22	333	1.7
Esophagus	150	32	14	28	32	5	19	81	9	220	1.1
Stomach	151	22	9	31	44	8	25	64	15	218	1.1
Intestine, except rectum	152,153	69	31	130	156	18	52	217	49	722	3.6
Rectum and anal canal	154	125	24	77	92	23	48	316	33	738	3.7
Other digestive system	155-159	41	11	40	51	8	34	79	29	293	1.5
Nose, middle ear and accessory sinuses	160	9	2	9	9	1	6	23	2	61	0.3
Larynx	161	45	18	59	48	5	38	164	13	390	2.0
Lung, bronchus and trachea	162	440	162	440	436	85	437	1,008	134	3,142	15.8
Other respiratory	163-165	4	–	11	16	3	8	10	2	54	0.3
Bone	170	6	2	15	9	2	4	18	4	60	0.3
Malignant melanoma	172	86	14	50	67	5	160	138	24	544	2.7
Other cancer of skin	173	340	197	368	191	53	335	519	116	2.119	10.7
Breast	174,175	475	170	401	506	78	264	1.358	178	3,430	17.3
Cervix uteri	180	57	20	48	55	11	20	195	14	420	2.1
Other uterus	179,181,182	145	27	102	93	14	24	230	25	660	3.3
Ovary, tubes and ligament	183	94	27	58	55	14	28	209	18	503	2.5
Other female genital organs	184	18	5	13	18	–	11	29	4	98	0.5
Prostate	185	150	49	121	111	23	104	298	30	886	4.5
Testis	186	26	8	21	35	4	20	89	7	210	1.0
Other male genital organs	187	1	2	1	1	–	3	9	2	19	0.1
Bladder	188	53	28	49	78	15	48	129	15	415	2.1
Kidney and other urinary	189	35	17	32	43	8	13	90	13	251	1.3
Brain and nervous system	191,192	56	18	79	68	12	36	167	12	448	2.2
Thyroid gland	193	14	–	8	11	2	4	33	1	73	0.4
Lymphosarcoma and reticulum-cell sarcoma	200	35	21	60	45	8	35	183	24	411	2.1
Hodgkin's disease	201	27	14	28	40	4	15	105	10	243	1.2
Other lymphomas	202	80	15	55	67	8	36	115	18	394	2.0
Leukemia	204-208	72	14	77	36	13	7	213	29	461	2.3
Other sites	Residual	553	48	126	140	27	111	424	50	1,479	7.4
TOTAL		3,219	1,013	2,658	2,667	472	2,037	6,870	934	19,870	100.0
Cervix uteri (in situ)	233.1	4	2	5	6	1	2	15	3	38	...
Other sites (in situ)	230-234	39	27	59	56	7	71	82	21	362	...
Neoplasms of uncertain behaviour	235-238	40	11	38	17	5	7	61	16	195	...
Multiple skins (see text)	173	200	187	325	189	21	149	315	82	1,468	...
Seen at more than one centre		5	40	38	76	9	30	115	10	323	

*Provisional (transition period — see text)

[1] ICD9 — International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

TABLE X*

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1985

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Algoma	1	—	6	2	4	4	157	1	175
Brant	212	—	10	—	—	1	3	2	228
Bruce	5	—	98	—	—	2	43	—	148
Carleton	1	2	2	1,417	—	6	8	1	1,437
Cochrane	4	3	2	29	8	5	130	1	182
Dufferin	—	—	—	—	—	6	66	—	72
Dundas	—	6	—	35	—	—	—	—	41
Durham[3]	1	—	1	1	—	61	346	1	411
Elgin	1	—	184	—	—	—	—	—	185
Essex	2	—	57	—	—	—	5	867	931
Frontenac	1	307	5	2	—	2	10	—	327
Glengarry	—	5	—	50	—	—	—	—	55
Grenville	1	31	—	40	—	—	1	—	73
Grey	4	3	58	—	—	4	115	—	184
Haldimand-Norfolk[1]	162	—	53	—	—	4	3	—	222
Haliburton	—	—	—	2	—	4	21	—	27
Halton	270	—	1	1	—	12	169	1	454
Hastings	2	212	—	5	—	16	63	—	298
Huron	1	—	132	—	—	1	6	—	140
Kenora	—	1	1	—	26	1	7	—	36
Kent	—	—	220	—	—	—	—	33	253
Lambton	1	1	275	—	—	1	4	—	282
Lanark	—	33	2	72	—	—	—	—	107
Leeds	—	155	—	14	—	2	4	—	175
Lennox and Addington	—	82	—	8	—	—	8	—	98
Manitoulin	1	—	—	—	—	—	24	—	25
Middlesex	3	—	782	—	—	—	11	—	796
Muskoka	7	—	—	1	—	19	75	—	102
Niagara[1]	771	—	3	—	—	17	107	—	898
Nipissing	1	—	4	7	1	3	195	1	212
Northumberland[2]	3	29	—	1	—	20	112	—	165
Oxford	6	—	230	1	—	1	4	—	242
Parry Sound	2	1	1	—	—	6	69	—	79
Peel	4	—	2	1	—	68	599	1	675
Perth	—	—	160	1	—	3	8	—	172

TABLE X* (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1985

COUNTY OR DISTRICT	TREATMENT CENTRE							Windsor	TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto			
						Bayview	PMH		
Peterborough[3]	1	1	–	–	–	9	200	–	211
Prescott	–	–	–	52	–	–	–	–	52
Prince Edward	1	65	–	–	–	4	6	–	76
Rainy River	–	–	–	–	47	–	3	–	50
Renfrew	1	1	–	207	–	–	3	–	212
Russell	–	–	2	63	–	–	1	–	66
Simcoe[3]	2	–	3	3	–	106	362	–	476
Stormont	–	8	1	162	–	–	–	–	171
Sudbury	3	1	1	6	–	5	270	1	287
Thunder Bay	5	–	2	–	383	7	29	–	426
Timiskaming	2	–	3	6	–	5	72	–	88
Victoria[3]	–	–	1	–	–	18	115	–	134
Waterloo	45	–	260	1	–	7	59	–	372
Wellington	166	–	18	–	–	6	49	–	239
Wentworth	1,082	–	2	7	–	1	12	1	1,105
York	9	2	10	4	–	1,439	3,152	1	4,617
Quebec	7	5	2	415	–	3	26	1	459
Other Provinces	8	6	8	26	2	5	72	3	130
U.S.A.	2	27	9	8	1	15	12	8	82
Other World	2	–	–	7	–	23	53	5	90
Residence at diagnosis not stated	416	26	47	10	–	115	1	5	620
TOTAL	3,219	1,013	2,658	2,667	472	2,037	6,870	934	19,870

*Provisional (transition period — see text).

[1] In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

[2] In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.

[3] In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

presentatives of the Ministries of Health and Labour, Health and Welfare Canada, OCTRF Regional Cancer Centres, NCIC, the Ludwig Institute, and the Ontario Cancer Institute.

Dr. Loraine D. Marrett introduced the program and discussed the data being generated by the Ontario Cancer Registry. Drs. Nancy Kreiger, Bernard Choi and Eric Holowaty discussed studies which use data from the Registry. Drs. Norman Boyd and Gail McKeown-Eyssen described clinical trials studying factors in the diet.

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We extend a special thanks to the directors of the regional cancer centres and the OCI/PMH and their managers of health records for support during the year, and to the members of the Foundation's Standing Committee on Records and Statistics and its sub-committees.

We acknowledge with gratitude the assistance of all the staff of Information Systems in the processing of the Foundation's large data base. In particular, we thank the individuals working under the direction of Mrs. June Murphy and Mr. Tom Broz, who have generated incidence data up to and including 1984.

Our special thanks are extended to Mrs. Mary Nemes, Manager of Health Records in the Division, Miss Darlene Dale, Supervisor of Cancer Registry Records, and the staff of the Division for their dedication to the generation of incidence data and their continual effort to improve the quality of the Ontario Cancer Registry. We are also grateful to Mmes. Margaret Holman and Sheila Wing for their help in preparing this report and to the staff of the Epidemiology Research Unit at the University of Toronto.

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APPENDICES

APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling $1,956,452 for the fiscal year ending March 31, 1986, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received during the above period from the following estates:

The late Annie M.S. Abbott, Toronto	$ 2,688
— Robert Hugh Ball, Strathroy for research at London Centre	5,832
— Nova Arthur Belanger, Barrie	2,500
— Elsie Torrance Bethune, Hamilton for research	1,000
— Alice Vera Birch, Etobicoke	33,435
— Grace Leona Brooker, Leamington	5,000
— George Rae Browne, Toronto	8,082
— Jessie Madge Browne, Toronto	5,723
— Ada May Brunner, Thamesville for research at London Centre	81,032
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— Ruby Laura Winnifred Dolan, Owen Sound	1,000
— Dorothy Evelyn Douglas, Thunder Bay	62,076
— Anne Ellen Downes, London for research at London Centre	5,412
— Eldred Durham, Toronto (Anne and Eldred Durham Trust Fund) for research	8,304
— John Jacob Freedman, Toronto	6,500
— Gertrude Lillian Garbutt, Toronto	300,000
— Gordon C. Garbutt, Toronto	250,000
— Esther Ann Gibson, Township of West Flamborough, Wentworth County for use at Hamilton Centre	5,000

– Erna Zoe Louise Goering, Hamilton for research at Hamilton Centre	2,500
– William Charles James, Toronto	1,000
– Boyd E.W. Kipkie, Township of Kingston County of Frontenac	200,000
– Pearl Audrey Kokesch, Brussels for research	46,949
– Eleanor Robertson Kress, Listowel	9,143
– Reginald J. Lewis, Toronto	11,688
– Edna Doris Lowe, Toronto	15,000
– Elizabeth Annie Marchment, Brampton	77,392
– Lilyan Ann Matthews, Etobicoke	10,000
– Lila Myers, Oshawa for research	10,199
– Elanor Florence McCarthy, Brampton for research	1,000
– Robert Sutherland McDonald, Toronto	18,000
– Marjorie Beatrice Palk, Scarborough	2,000
– Dora Elizabeth Potter, Spalding Lincs. England for research at Hamilton Centre	37,553
– Harriet M. Quantz, Richmond Hill	2,000
– Helen Jane Rennie, London for use at London Centre	13,157
– John Renton, Toronto	1,680
– Bertha M. Richter, London (Richter Endowment Fund Trust) in memory of Martha Ann Richter and George Richter for use at London Centre	139,500
– Clara B. Sanderson, Brantford (John A. Sanderson and Family Trust)	9,111
– Alfred Strathdee, London for use at London Centre	15,414
– Beatrice M. Tufts, Amherstburg for use at Windsor Centre	5,314
– Louisa A. Turner, Scarborough	2,719
– Una Adelaide Upthgrove, London for research at London Centre	1,763
– Eula White, London for use at London Centre	1,000
– Gordon Thomas Whybrow, Hamilton	1,000
– George Hall Wilson, Brampton	65,440

— Madeleine Wilson, St. Marys (L.W. Wilson Trust) for research at London Centre	1,515
— Mabel Wright, Willowdale for research	25,000

Donations of $1,000 or more were received from the following:

— Adria Laboratories of Canada Ltd., Hamilton for use at Hamilton Centre	1,400
— Mrs. Bessie Armstron, Mount Pleasant for use at Hamilton Centre	1,000
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— Owen R. Chapman, Toronto	1,500
— Cyanamid Canada Inc., Waterloo for use at London Centre	1,000
— James Dennett, Corunna for research at London Centre	1,000
— Dreams Never Die, Ottawa (softball tournament) for use at Ottawa Centre	2,366
— James E. Dunn, Nepean for use at Ottawa Centre	1,000
— John Grand, Toronto for research at Toronto-Bayview Centre	1,500
— J. Leo Grant, Thorold for use at Hamilton Centre	2,000
— Hamilton Radiotherapy Associates Group Dr. R.G.C. MacLaren Memorial Fund	2,700
— Raymond N. James, Thunder Bay for use at Thunder Bay Centre	1,000
— Ian Kennedy, Cornwall one-half for use at Maurice Grimes Lodge one-half for use at Ottawa Centre	1,000
— M. Suzanne Kenny, Buckingham, P.Q. for use at Ottawa Centre	1,000
— The Kiwanians, Ottawa for equipment in Chemotherapy Unit at Ottawa Centre	1,807
— Knockers Club of Canada, Ottawa for residents' education fund at Ottawa Centre	1,000

– Verna Linkewich, Thunder Bay for use at Thunder Bay Centre	1,000
– Bertha M. Laidlaw, Windsor for use at Windsor Centre	1,000
– Louise May, Jasper, Ontario for use at Maurice Grimes Lodge	3,000
– Marquis, Trottier & Lambert, Aylmer, P.Q. for research at Ottawa Centre	2,237
– Muribar Investments, Toronto for special services to patients at Kingston Centre	5,000
– Schwartz Foods Cookie Haus, Cambridge for use at Thameswood Lodge	2,000
– Dr. R.S. Shearer and Associates, London for palliative care at London Centre	7,634
– Ila M. Stewart, London for research at London Centre	5,000
– Robert Thomson, St. Clair Beach for use at Windsor Centre	4,000
– The Toronto Star, Toronto	2,000
– William E. White, Ottawa for use at Ottawa Centre	1,000
– H. Wrigglesworth, Don Mills (Dorothy Wrigglesworth Cancer Research Fund)	1,000

The Foundation is grateful to these donors and to the many others not listed above and it reveres the memory of those who, when making their wills, extended beyond their lifetime fight against cancer. These welcome additions to our research program and other funds ensure that the Foundation's extensive research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED IN 1985 BY CAREER SCIENTISTS, RESEARCH ASSOCIATES, GRANTEES, MEMBERS OF THE OCTRF STAFFS AT THE REGIONAL CANCER CENTRES AND HEAD OFFICE AND THE OCI/PMH

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Capital renewal is more than "bricks and mortar" — it calls for the community's full and continued support of the many kinds of health-care professionals who daily carry on the fight against cancer across Ontario